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A 63-year-old woman is hospitalized because of dyspnea on exertion and generalized fatigue. She has been hospitalized 3 times during the past year for heart failure exacerbations. Her other medical problems include essential hypertension for 20 years, myocardial infarction at the age of 58, and hypercholesterolemia. She has a 36-pack-year smoking history in addition to a 10-year history of alcohol abuse. Physical examination reveals tachycardia, distended neck veins, bilateral crackles on lung auscultation, a third heart sound on cardiac auscultation, and pedal edema. The appropriate therapy is initiated. On the third day of hospitalization, her hematocrit level increases to 50%, up from 44% on admission. An arterial blood gas analysis shows an arterial O_2 partial pressure (PaO_2) of 70 mm Hg. A ^{51}Cr-tagged red blood cell infusion indicates normal red blood cell mass. Which of the following is the most likely cause of this patient's polycythemia?

A. Polycythemia vera
B. Hypoxic erythrocytosis
C. Renal disease
D. Occult neoplasia

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A. Polycythemia vera
B. Hypoxic erythrocytosis
C. Renal disease
D. Occult neoplasia
E. Relative erythrocytosis

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hypercholesterolemia. She has a 36-pack-year smoking history in addition to a 10-year history of alcohol abuse. Physical examination reveals tachycardia, distended neck veins, bilateral crackles on lung auscultation, a third heart sound on cardiac auscultation, and pedal edema. The appropriate therapy is initiated. On the third day of hospitalization, her hematocrit level increases to 50%, up from 44% on admission. An arterial blood gas analysis shows an arterial O_2 partial pressure (PaO_2) of 70 mm Hg. A ^{51}Cr-tagged red blood cell infusion indicates normal red blood cell mass. Which of the following is the most likely cause of this patient's polycythemia?

A. Polycythemia vera (3%)
B. Hypoxic erythrocytosis (48%)
C. Renal disease (5%)
D. Occult neoplasia (1%)
E. Relative erythrocytosis (41%)

Correct

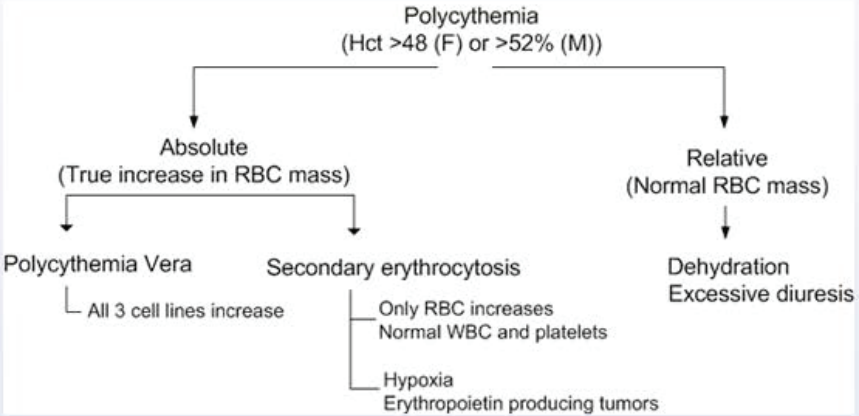
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Last Updated

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Polycythemia (erythrocytosis) is defined as a hematocrit level > 52% in men and > 48% in women. It may be the result of a true increase in the red blood cell (RBC) mass (absolute erythrocytosis) or decrease in the plasma volume (relative erythrocytosis).



In a patient with erythrocytosis, the following tests can help determine the cause:

1. **Absolute versus relative erythrocytosis**: Hemoglobin and hematocrit levels cannot accurately differentiate these conditions. Direct measurement of the RBC mass is necessary. An increased total RBC mass indicates an absolute erythrocytosis; a normal RBC mass indicates a relative

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1. **Absolute versus relative erythrocytosis**: Hemoglobin and hematocrit levels cannot accurately differentiate these conditions. Direct measurement of the RBC mass is necessary. An increased total RBC mass indicates an absolute erythrocytosis; a normal RBC mass indicates a relative erythrocytosis. This patient does not have an increased RBC mass and is likely experiencing relative erythrocytosis due to aggressive diuretic therapy for her heart failure exacerbation.

2. **Primary versus secondary erythrocytosis**: Serum erythropoietin levels can be used to differentiate primary from secondary erythrocytosis. Primary erythrocytosis is associated with low erythropoietin levels and is caused by myeloproliferative disorders such as polycythemia vera. Secondary erythrocytosis is characterized by increased erythropoietin levels due to chronic hypoxia from high altitudes, smoking, or chronic obstructive pulmonary disease; or abnormal secretion by neoplastic or otherwise diseased tissues.

3. **Hypoxic versus other causes of secondary erythrocytosis**: Measurement of the arterial oxygen saturation (SaO_2) is important to exclude hypoxemia as a cause of the erythrocytosis. SaO_2 < 92% (PaO_2 < 65 mm Hg) can cause secondary polycythemia. SaO_2 (measured as a percentage) should not be confused with PaO_2 (measured as a partial pressure in mm Hg).

(Choice A) Polycythemia vera is a myeloproliferative disorder associated with marked erythrocytosis and

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be confused with PaO_2 (measured as a partial pressure in mm Hg).

(Choice A) Polycythemia vera is a myeloproliferative disorder associated with marked erythrocytosis and more modest increases in granulocytes and platelets. A low erythropoietin level is characteristic, along with increased RBC mass.

(Choice B) Hypoxia is a common cause of secondary erythrocytosis. $SaO_2 < 92\%$ ($PaO_2 < 65$ mm Hg) appears to be the threshold for the development of secondary erythrocytosis. This patient has hypoxemia above this threshold, an acute (< 3 day) increase in hematocrit, and normal RBC mass; none of these features are consistent with hypoxemia-induced erythrocytosis.

(Choices C and D) Occasionally, renal disease or occult neoplasia can cause secondary erythrocytosis due to abnormal erythropoietin production by the diseased tissue. Work-up will reveal an increased RBC mass and an increased erythropoietin level. However, chronic renal disease typically leads to decreased erythropoietin production.

Educational objective:
Erythrocytosis is defined as a hematocrit level > 52% in men and > 48% in women. Measurement of red blood cell mass is necessary to distinguish absolute from relative erythrocytosis. A normal red blood cell mass indicates plasma volume contraction as the cause of polycythemia.

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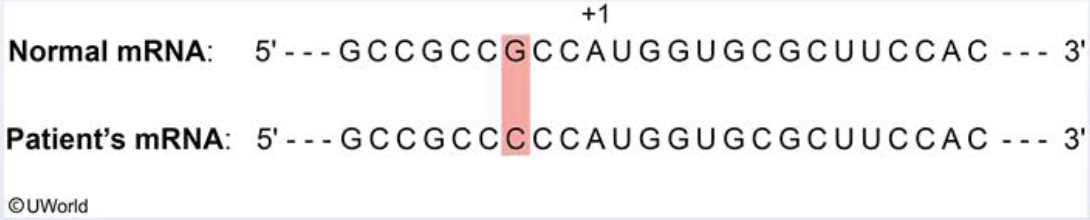
Educational objective:
Erythrocytosis is defined as a hematocrit level > 52% in men and > 48% in women. Measurement of red blood cell mass is necessary to distinguish absolute from relative erythrocytosis. A normal red blood cell mass indicates plasma volume contraction as the cause of polycythemia.

References

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The following vignette applies to the next **2** items. The items in the set must be answered in sequential order. Once you click **Proceed to Next Item**, you will not be able to add or change an answer.

A 16-year-old girl with a history of anemia since childhood is evaluated for a genetic abnormality after several members of her family are also found to be anemic. It is determined that she has a point mutation in the β globin gene, which has resulted in the substitution of guanine (G) with cytosine (C) in the mRNA sequence shown below (+1 position indicates start codon).



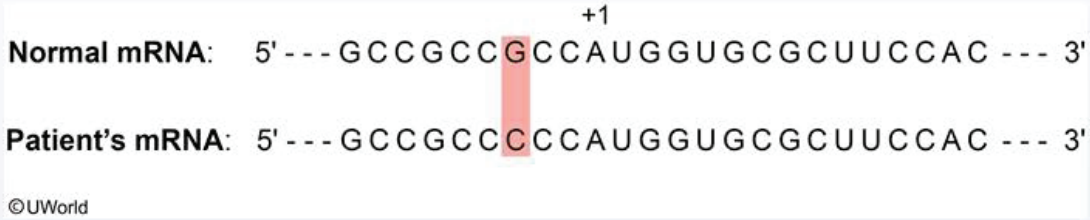
Item 1 of 2

Which of the following cellular processes is most likely impaired due to this patient's gene mutation?

A. Co-translational protein targeting to endoplasmic reticulum (21%)

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sequence shown below (+1 position indicates start codon).



Item 1 of 2

Which of the following cellular processes is most likely impaired due to this patient's gene mutation?

A. Co-translational protein targeting to endoplasmic reticulum (21%)

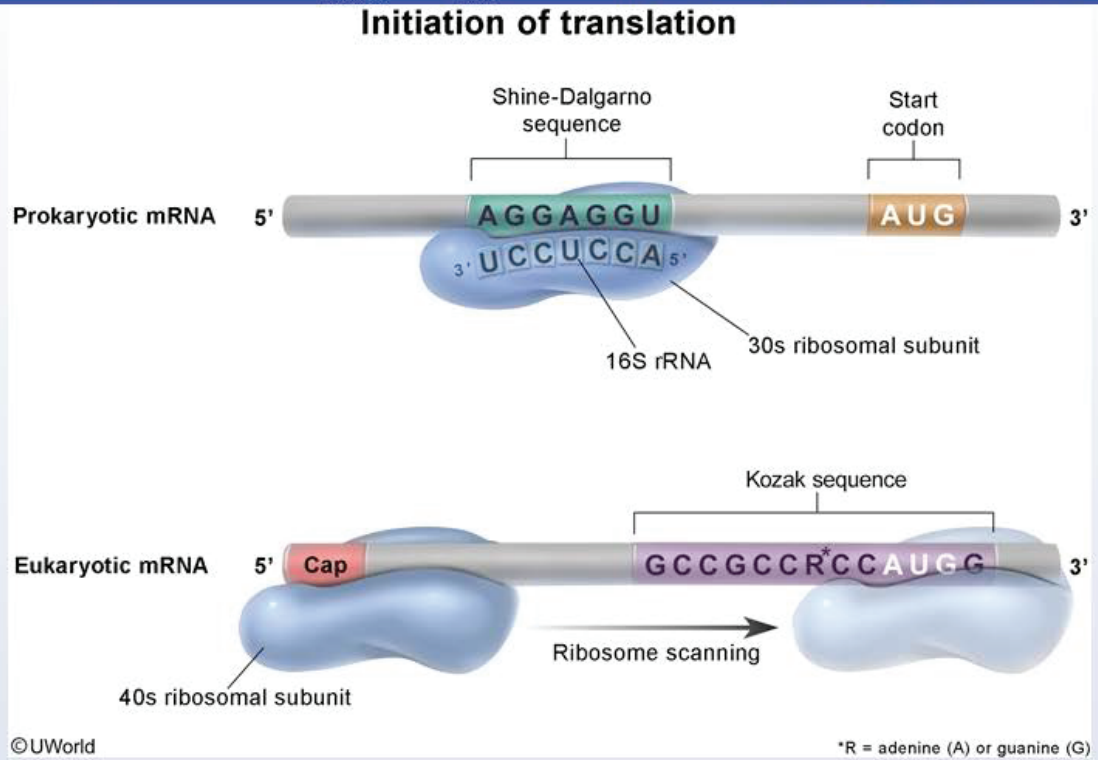
✓ B. Initiation of translation (52%)

C. Peptide bond formation (11%)

D. Ribosomal translocation during polypeptide elongation (10%)

E. Termination of polypeptide synthesis (4%)

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This patient has β thalassemia due to a **mutation** in the β globin gene **just before the methionine start codon** (AUG) that is most likely disrupting translation initiation. Eukaryotic translation initiation requires the

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*R = adenine (A) or guanine (G)

This patient has β thalassemia due to a **mutation** in the β globin gene **just before the methionine start codon** (AUG) that is most likely disrupting translation initiation. Eukaryotic translation initiation requires the assembly of ribosomal subunits (60S and 40S), mRNA, initiation factors, initiator tRNA charged with methionine, and guanosine-5'-triphosphate (GTP).

The small ribosomal subunit (40S) initially binds to the 5' cap of mRNA and scans for the start codon, which is positioned near the beginning of the mRNA and is surrounded by the **Kozak consensus sequence**. This short sequence identifies the specific AUG codon that serves as the **initiator of translation** (analogous to the Shine-Dalgarno sequence in bacteria).

Mutations affecting the Kozak consensus sequence can significantly **impair protein translation** and have been identified in patients with α and β thalassemias.

(Choice A) Co-translational protein targeting is mediated by the N-terminal amino acid sequence of an elongating polypeptide. This localization signal is recognized by a signal recognition protein that helps transport the ribosome to the rough endoplasmic reticulum (ER). Mutations affecting the signal sequence would be found after the start codon (AUG).

(Choice C) Peptide bond formation is catalyzed by peptidyl transferase, an RNA enzyme ("ribozyme") that

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transport the ribosome to the rough endoplasmic reticulum (ER). Mutations affecting the signal sequence would be found after the start codon (AUG).

(Choice C) Peptide bond formation is catalyzed by peptidyl transferase, an RNA enzyme ("ribozyme") that resides in the large ribosomal subunit. A defect in rRNA coding for ribosomes would interfere with this process.

(Choice D) During polypeptide elongation, the ribosome moves 3 nucleotides toward the 3' end of mRNA, advancing peptidyl tRNA from the A site to the P site (translocation). Translocation is catalyzed by elongation factor 2 and requires GTP hydrolysis.

(Choice E) Termination of polypeptide synthesis occurs at stop codons. Mutations in stop codons (nonstop mutations) can result in continued and inappropriate translation of mRNA into the 3'-untranslated region, producing an excessively long, nonfunctional polypeptide.

Educational objective:

The Kozak consensus sequence occurs on eukaryotic mRNA and helps initiate protein translation by identifying the proper methionine start codon (AUG).

References

- Diversity of preferred nucleotide sequences around the translation initiation codon in eukaryote

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Item 2 of 2

The patient's genetic defect has resulted in decreased β globin chain synthesis. Which of the following is most likely to be seen on laboratory testing?

- A. Hyperchromia (3%)
- B. ~~Iron deficiency~~ (4%)
- ✓ C. Microcytosis (77%)
- D. ~~Red blood cell sickling~~ (8%)
- E. ~~Spherocytosis~~ (5%)

Correct

77% Answered correctly

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01/04/2021 Last Updated

Explanation

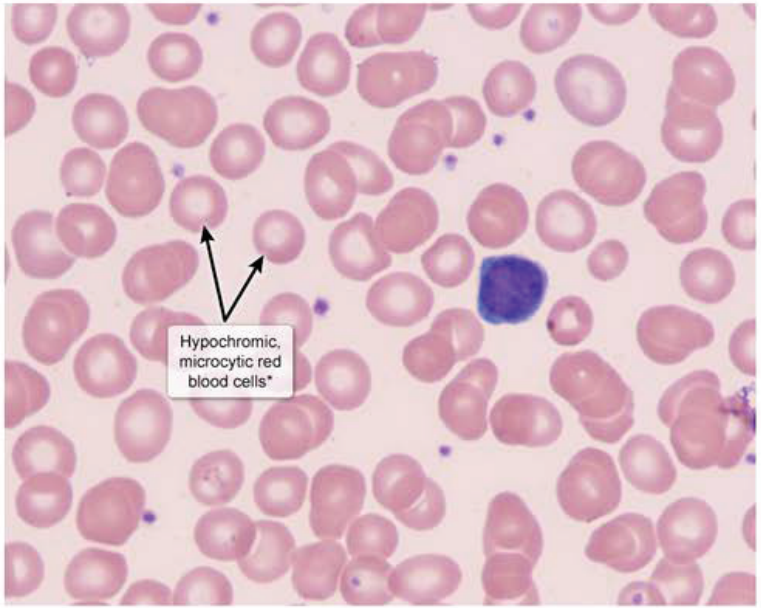
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Beta thalassemia

Exhibit Display

Beta thalassemia



*Pale, small red blood cells

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*Pale, small red blood cells

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Patients with **β thalassemia** have decreased β globin chain synthesis, which causes **hypochromic, microcytic anemia** (mean corpuscular volume <80 μm^3). **Reduced β globin synthesis** also results in the precipitation of unpaired α chains within red cells, causing membrane damage. This subsequently leads to the death of red cell precursors in the bone marrow (ineffective erythropoiesis) and lysis of circulating erythrocytes (hemolysis).

Normal erythrocytes have an area of central pallor that typically measures 1/3 of the cell diameter. Patients with β thalassemia classically have blood smears showing small red cells with an increased area of central pallor, as seen in the image above. Other common findings include anisopoikilocytosis (variation in size and shape), target cells, nucleated red cell precursors, and basophilic stippling.

(Choices A and E) Hyperchromia is characterized by reduced central pallor due to increased hemoglobin concentration and is usually associated with spherocytosis. Hereditary spherocytosis is caused by a variety of molecular defects in the genes that encode certain red cell membrane proteins (eg, spectrin, ankyrin, band 3, protein 4.2).

(Choice B) Iron deficiency often leads to hypochromic, microcytic anemia and is commonly caused by chronic, asymptomatic bleeding (eg, slow gastrointestinal bleed, abnormal menstruation). In contrast,

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(Choices A and E) Hyperchromia is characterized by reduced central pallor due to increased hemoglobin concentration and is usually associated with spherocytosis. Hereditary spherocytosis is caused by a variety of molecular defects in the genes that encode certain red cell membrane proteins (eg, spectrin, ankyrin, band 3, protein 4.2).

(Choice B) Iron deficiency often leads to hypochromic, microcytic anemia and is commonly caused by chronic, asymptomatic bleeding (eg, slow gastrointestinal bleed, abnormal menstruation). In contrast, patients with thalassemia often have iron overload, not iron deficiency.

(Choice D) Red blood cell sickling occurs in sickle cell anemia, which is caused by an A to T mutation in the β globin gene that results in glutamate being substituted with valine at position 6.

Educational objective:

β thalassemia results in hypochromic, microcytic anemia due to decreased β globin chain synthesis. Unpaired α chains precipitate within red cells and cause membrane damage, leading to ineffective erythropoiesis and hemolysis.

References

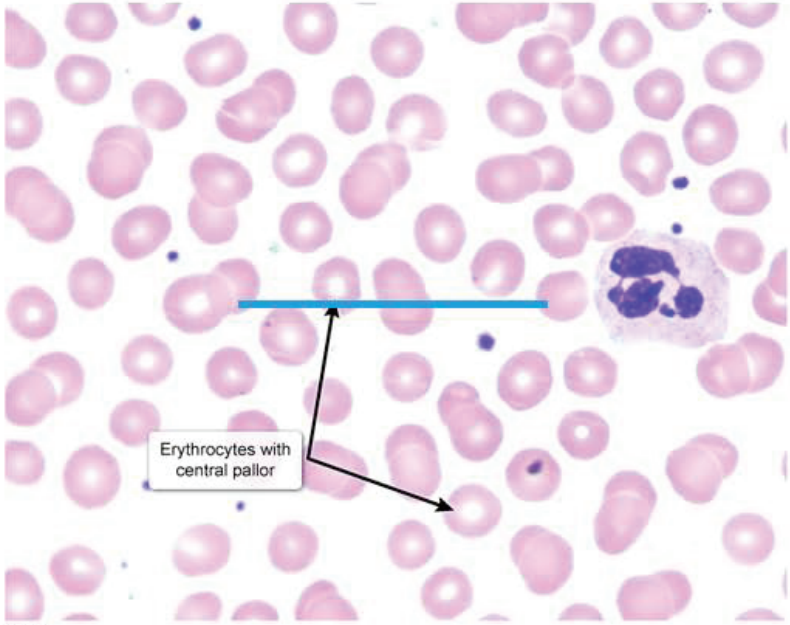
- Alpha and beta thalassemia.

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Normal peripheral blood smear



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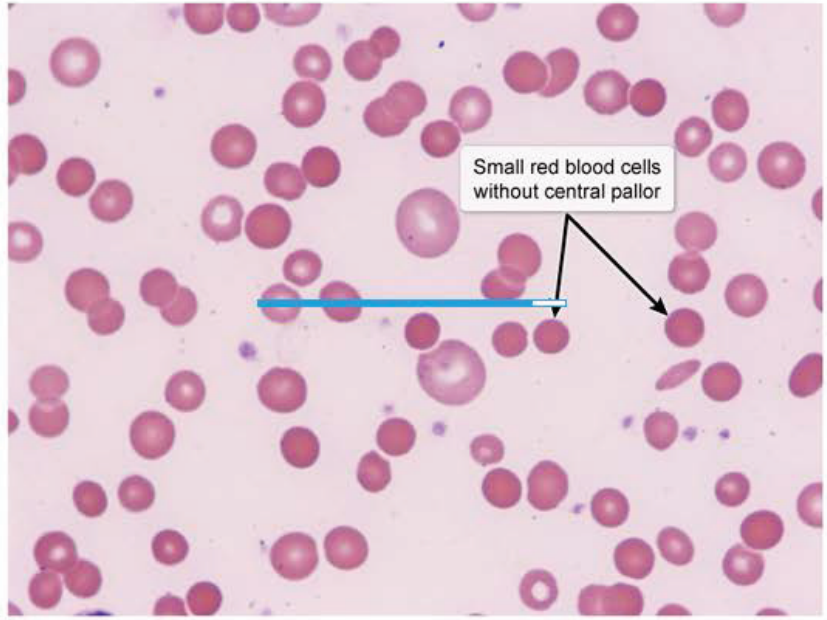
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the death of red cell precursors in the bone marrow (ineffective erythropoiesis) and lysis of circulating

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Spherocytes



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Educational objective:

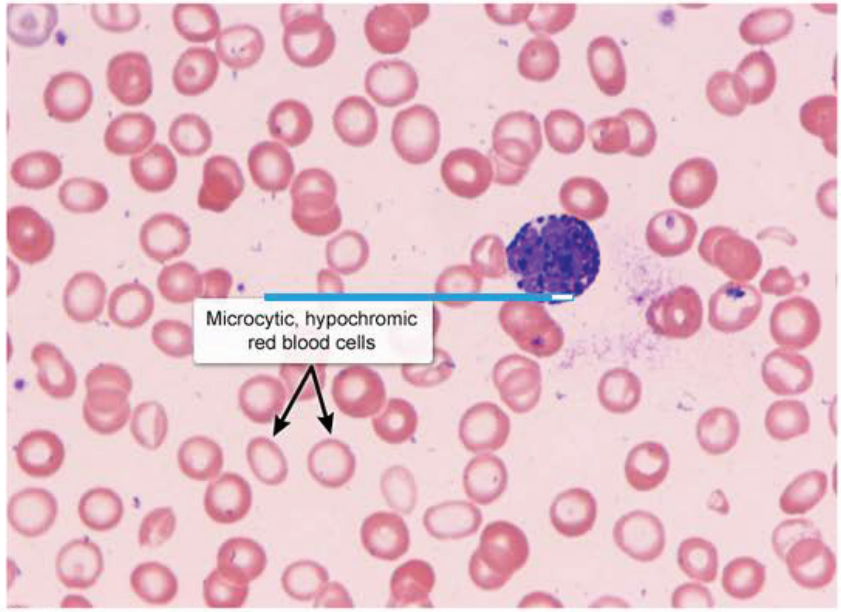
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the death of red cell precursors in the bone marrow (ineffective erythropoiesis) and lysis of circulating

Exhibit Display

Iron deficiency anemia



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Educational objective:

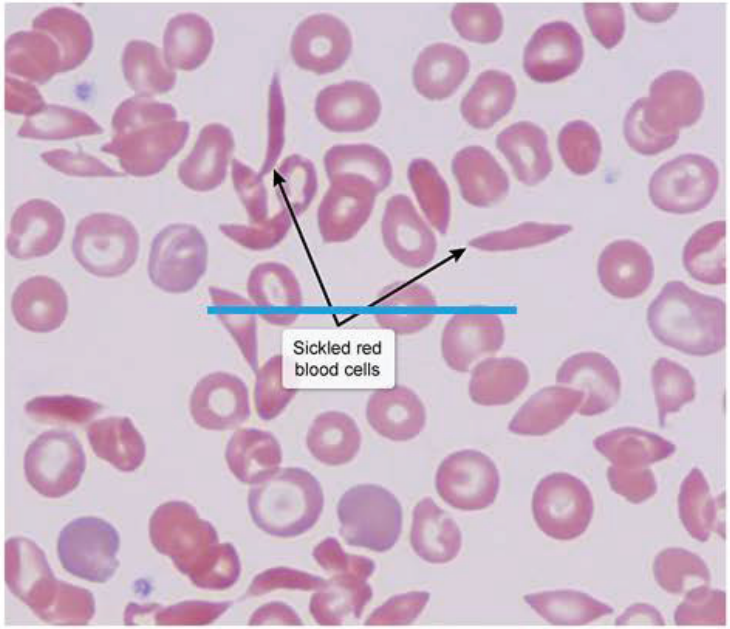
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the death of red cell precursors in the bone marrow (ineffective erythropoiesis) and lysis of circulating

Exhibit Display

Sickle cell disease



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Educational objective:

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A 59-year-old woman comes to the office due to progressive fatigue and occasional heart palpitations over the last 6 months. The patient has been under a lot of stress recently due to problems at work. She has no dietary restrictions, eats out at restaurants frequently, and drinks 2 or 3 cans of beer on the weekends. The patient is postmenopausal and has not noticed any uterine bleeding, dark stools, or bleeding with bowel movements. Her BMI is 25 kg/m^2. Hemoglobin is 8.5 g/dL. Peripheral blood smear reveals pale, microcytic erythrocytes. Which of the following is the most likely underlying cause of this patient's abnormal laboratory findings?

A. Drug abuse
B. Hematologic malignancy
C. Hemolysis
D. Liver disease
E. Occult blood loss
F. Poor nutrition

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A. Drug abuse (2%)
B. Hematologic malignancy (4%)
C. Hemolysis (4%)
D. Liver disease (3%)
✓ E. Occult blood loss (45%)
F. Poor nutrition (39%)

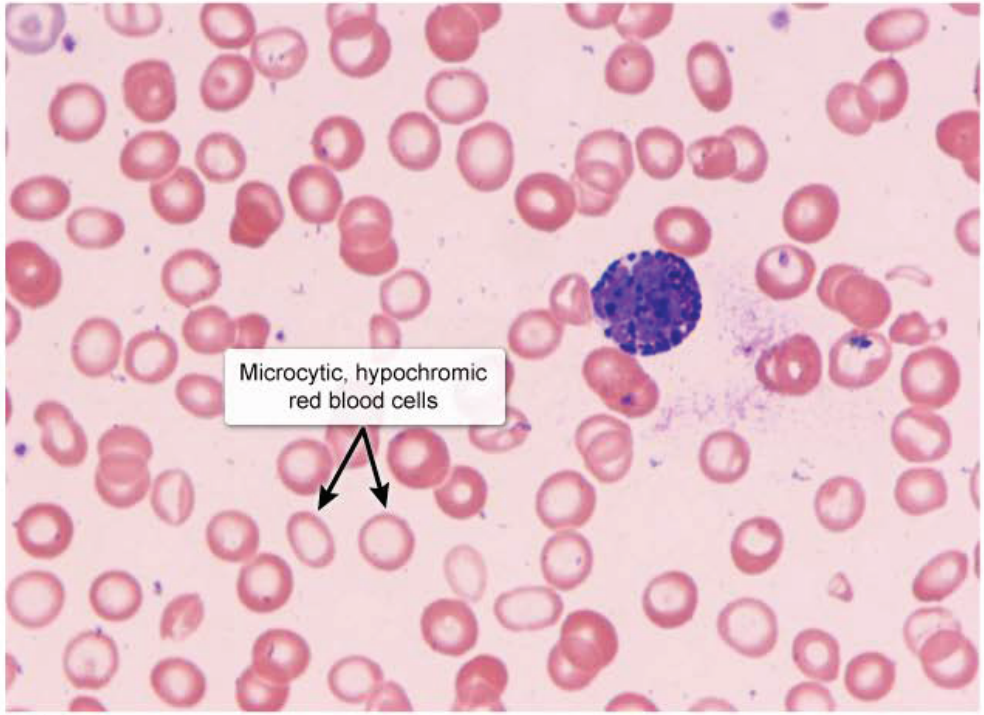
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Iron deficiency anemia



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Fatigue and heart palpitations are common manifestations of all forms of anemia. This patient's peripheral smear findings indicate **hypochromic, microcytic anemia**, which **most often** arises in the setting of **iron deficiency**. The primary, and most dangerous if overlooked, mechanism of iron deficiency is **blood loss**, and it should be excluded first. Women of childbearing age are commonly iron deficient due to menstruation. Men (especially over the age of 60) or postmenopausal women have no physiologic reason to be iron deficient and therefore should be evaluated for blood loss in the **gastrointestinal (GI) tract** (eg, due to malignancy). GI blood loss is often **occult**, so the lack of dark or bright red stools in this patient should not rule out GI hemorrhage. Iron studies (including ferritin) should be obtained, and the patient will likely require endoscopic evaluation.

(Choice A) Ingestion of the more commonly abused drugs is not associated with microcytic anemia.

(Choice B) Hematologic malignancies (eg, leukemia, lymphoma, multiple myeloma) tend to be associated with normochromic, normocytic anemia. The decrease in erythropoiesis seen in these patients results from hypersplenism or tumor replacement of bone marrow mass.

(Choice C) Hemolysis often presents with a normochromic, normocytic anemia. Spherocytes or schistocytes are often seen on peripheral blood smear.

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with normochromic, normocytic anemia. The decrease in erythropoiesis seen in these patients results from hypersplenism or tumor replacement of bone marrow mass.

(Choice C) Hemolysis often presents with a normochromic, normocytic anemia. Spherocytes or schistocytes are often seen on peripheral blood smear.

(Choice D) The anemia of chronic liver disease is usually normocytic or slightly macrocytic with target cells on the peripheral blood smear. Microcytic anemia occurs in <25% of cases, and most patients have only mild anemia with a hemoglobin level of 10-11 g/dL.

(Choice F) This patient has a normal BMI and no factors predisposing her to malnutrition (eg, dietary restrictions, chronic alcoholism). A normal Western diet provides 6 mg of iron for every 1,000 calories, and the recommended intake for individuals age >50 is 8 mg per day. As a result, men and postmenopausal women (ie, not menstruating, pregnant, or lactating) usually have no dietary iron shortage.

Educational objective:
Hypochromic, microcytic anemia is most commonly due to iron deficiency. Blood loss, especially occult loss from the gastrointestinal tract, must be ruled out in a patient with iron deficiency anemia.

Pathology Hematology & Oncology Iron deficiency anemia

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A 67-year-old man is evaluated for persistent lower back pain and fatigue. The patient has no other medical conditions and takes no medications. Laboratory testing shows anemia and renal dysfunction. Serum total protein levels are elevated, and electrophoresis of the serum proteins reveals a narrow spike in the gamma globulin region. A subsequent bone marrow biopsy shows abnormal marrow cells. A medication that blocks cellular proteasome action is administered. This treatment is most likely to cause which of the following effects on the abnormal cells?

A. Augmented cytotoxic T-cell response
B. Decreased DNA methylation
C. Impaired RNA splicing
D. Improved differentiation
E. Increased apoptosis

Submit

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A. Augmented cytotoxic T-cell response (12%)
B. Decreased DNA methylation (3%)
C. Impaired RNA splicing (15%)
D. Improved differentiation (9%)
E. Increased apoptosis (59%)

Incorrect
Correct answer
E

59%
Answered correctly

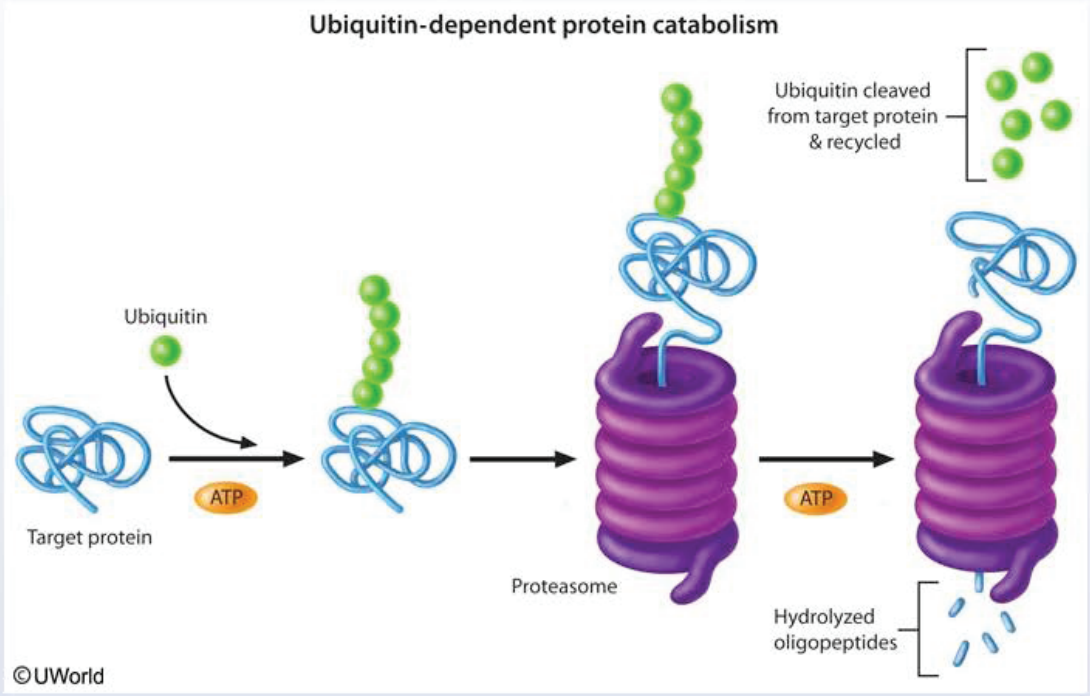
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Explanation



This patient's manifestations (anemia, back pain, renal insufficiency), monoclonal protein spike on

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This patient's manifestations (anemia, back pain, renal insufficiency), monoclonal protein spike on electrophoresis, and bone marrow findings indicate likely **multiple myeloma** (MM), a plasma cell malignancy associated with the overproduction of monoclonal immunoglobulins or IgG fragments (eg, IgG light chains). Treatment regimens for MM often incorporate medications that **block proteasome function** (eg, bortezomib).

The proteasome is a barrel-shaped structure with a proteolytic core that degrades ubiquitin-tagged proteins. Proteasome inhibition results in the **accumulation** of damaged and **misfolded proteins** that have a cytotoxic effect. MM cells are particularly susceptible to proteasome inhibition because they generate extremely high quantities of secretory proteins (eg, monoclonal immunoglobulins), some of which misfold and aggregate within the endoplasmic reticulum. Increased stress on the endoplasmic reticulum triggers an **unfolded protein response** that eventually leads to activation of caspases and **cellular apoptosis**.

(Choice A) Cytotoxic T-cell destruction of cancer cells is augmented by checkpoint inhibitor immunotherapies such as those that target the programmed cell death 1 receptor and CTLA-4. These drugs are often used in the treatment of MM but augmented cytotoxic T-cell function is not related to proteosome inhibition.

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drugs are often used in the treatment of MM but augmented cytotoxic T-cell function is not related to proteosome inhibition.

(Choice B) Azacitidine is a cytidine analogue that inhibits DNA methyltransferase. It reduces DNA methylation and alters gene expression, leading to reduced protein synthesis and increased cellular differentiation. It is toxic to abnormal hematopoietic cells but is used primarily to treat myelodysplastic syndrome.

(Choice C) RNA splicing is done by the nuclear spliceosome, which removes introns from transcribed pre-mRNA. The proteasome does not affect RNA splicing.

(Choice D) All-trans-retinoic acid is used in the treatment of acute promyelocytic leukemia. It works by promoting differentiation of neoplastic cells into mature neutrophils.

Educational objective:
Multiple myeloma, a plasma cell malignancy associated with significant production of secretory proteins (eg, monoclonal immunoglobulins), is frequently treated with proteasome inhibitors (eg, bortezomib). These drugs block the degradation of ubiquitinated proteins by the proteosome, which leads to accumulation of abnormally folded proteins that trigger cellular apoptosis.

References

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An elderly patient is diagnosed with aggressive non-Hodgkin's lymphoma. The tumor cells are shown to stain strongly for the CD20 marker. Which of the following biologic agents can be added to this patient's chemotherapy regimen to help improve the treatment response?

A. Infliximab
B. Rituximab
C. Interleukin-2
D. Imatinib
E. Abciximab

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An elderly patient is diagnosed with aggressive non-Hodgkin's lymphoma. The tumor cells are shown to stain strongly for the CD20 marker. Which of the following biologic agents can be added to this patient's chemotherapy regimen to help improve the treatment response?

A. Infliximab (6%)
B. Rituximab (72%)
C. Interleukin-2 (5%)
D. Imatinib (11%)
E. Abciximab (3%)

Correct

72%
Answered correctly

36 secs
Time Spent

01/30/2021
Last Updated

Explanation

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The class of treatments known as biologic response modifiers (BRMs) includes antibodies, cytokines and other substances intended to restore or induce the immune system's ability to overcome disease. All of the answer choices here are BRMs.

The patient described above has a lymphoma that expresses surface CD20, a B-cell marker. Rituximab is a monoclonal antibody used in lymphoma immunotherapy that specifically targets the CD20 surface immunoglobulin.

Another monoclonal antibody used in cancer treatment is trastuzumab (Herceptin), which is used in the treatment of breast cancer.

(Choice A) Infliximab is a chimeric (human/murine) IgG1 monoclonal antibody to TNF-alpha. This medication has had a significant impact on the management of rheumatoid arthritis. Infliximab is also used to treat ankylosing spondylitis and fistulizing Crohn's disease.

(Choice C) Interleukin-2 is a cytokine that regulates the activation and differentiation of T-cells to aid in tumor cell destruction. It is FDA-approved for the treatment of renal cell carcinoma and melanoma.

(Choice D) Diagnosis of CML requires the presence of the Philadelphia chromosome or the BCR/ABL fusion gene. Imatinib mesylate is a potent inhibitor of the BCR/ABL protein tyrosine kinase. It inhibits the

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to treat ankylosing spondylitis and fistulizing Crohn's disease.

(Choice C) Interleukin-2 is a cytokine that regulates the activation and differentiation of T-cells to aid in tumor cell destruction. It is FDA-approved for the treatment of renal cell carcinoma and melanoma.

(Choice D) Diagnosis of CML requires the presence of the Philadelphia chromosome or the BCR/ABL fusion gene. Imatinib mesylate is a potent inhibitor of the BCR/ABL protein tyrosine kinase. It inhibits the cellular proliferation of BCR/ABL-expressing cells without inducing apoptosis. This oral medication has dramatically changed the management of CML since its introduction.

(Choice E) Abciximab is a chimeric mouse-human monoclonal antibody against the platelet GP IIb/IIIa receptor. It works by blocking the final step in platelet aggregation. Abciximab is often administered during angioplasty in patients with acute coronary syndrome.

Educational Objective:
Rituximab is a monoclonal antibody directed against the CD20 antigen. Its introduction has improved the prognosis of some lymphomas.

Pharmacology	Hematology & Oncology	Nonhodgkin lymphoma
Subject	System	Topic

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A 1-year-old African American boy is brought to the emergency department by his parents with a 3-hour history of severe swelling and tenderness of the hands and feet. They do not know what caused the swelling and say that the boy cries when his hands or feet are touched. The patient has no history of recent illness and is up to date on all immunizations. The boy attends day care, but his parents are unsure about any sick contacts. His family history is significant for an older brother who died of pneumococcal sepsis at age 6. Physical examination shows bilateral, severe swelling of the hands and feet. Which of the following is most likely abnormal in this patient?

A. Left ventricular systolic function
B. Serum albumin
C. Serum C4 complement fraction
D. Serum haptoglobin
E. Systemic venous pressure
F. Urine cortisol excretion

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- A. Left ventricular systolic function
- B. Serum albumin
- C. Serum C4 complement fraction
- D. Serum haptoglobin
- E. Systemic venous pressure
- F. Urine cortisol excretion

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history of severe swelling and tenderness of the hands and feet. They do not know what caused the swelling and say that the boy cries when his hands or feet are touched. The patient has no history of recent illness and is up to date on all immunizations. The boy attends day care, but his parents are unsure about any sick contacts. His family history is significant for an older brother who died of pneumococcal sepsis at age 6. Physical examination shows bilateral, severe swelling of the hands and feet. Which of the following is most likely abnormal in this patient?

A. Left ventricular systolic function (2%)
B. Serum albumin (9%)
C. Serum C4 complement fraction (26%)
D. Serum haptoglobin (53%)
E. Systemic venous pressure (7%)
F. Urine cortisol excretion (1%)

Correct

53%
01 min, 11 secs
01/09/2021

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Sickle cell disease (SCD) is the most common autosomal recessive disorder in African Americans. Its manifestations include the following:

1. **Hemolysis:** Repeated sickling of red blood cells leads to permanent deformation and premature erythrocyte destruction by macrophages and mechanical stress. This causes **intra- and extravascular hemolysis**, resulting in increased indirect bilirubin and lactate dehydrogenase and **decreased haptoglobin**. Haptoglobin binds circulating hemoglobin and reduces renal excretion of free hemoglobin, preventing tubular injury.

2. **Vasoocclusive symptoms:** Patients with SCD may experience pain from hypoxic tissue injury and infarctions due to obstruction of small vessels by sickled cells. Microvascular occlusion typically involves the bone marrow, periosteum, and deep muscles but can occur in other organs. This patient is presenting with **dactylitis** (hand-foot syndrome), which results from small infarctions in the bones of the extremities. These infarctions cause swelling, tenderness, and warmth. Dactylitis is common in patients with SCD during the first few years of life as the affected bones still contain hematopoietic bone marrow. In older children and adults, vascular occlusion leads to pain crises, acute chest syndrome, leg ulceration, priapism, autosplenectomy, and stroke.

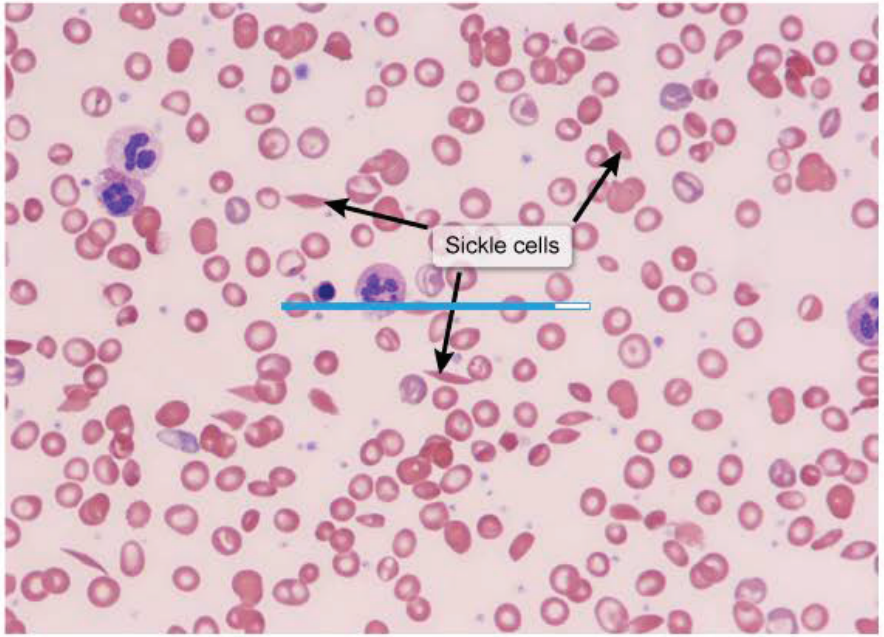
3. **Infections:** Patients with SCD are predisposed to infections with **encapsulated organisms** (eg,

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Exhibit Display

Sickle cell anemia in crisis



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5. Infections: Patients with SCD are predisposed to infections with **encapsulated organisms** (eg,

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3. **Infections:** Patients with SCD are predisposed to infections with **encapsulated organisms** (eg, *Streptococcus pneumoniae*) because repeated splenic infarcts cause functional asplenia.

(Choices A and E) The chronic anemia in SCD can result in cardiomegaly due to chronically increased cardiac output (systolic function is largely preserved due to an increase in stroke volume). However, this typically does not occur until after infancy. Older patients can develop congestive heart failure due to ischemic cardiomyopathy and present with decreased cardiac output and increased systemic venous pressure.

(Choices B and F) Serum albumin and urine cortisol excretion are typically normal in patients with SCD.

(Choice C) Hereditary angioedema is a rare autosomal dominant disorder that is associated with painless episodes of swelling involving the face, lips, larynx, and extremities. It is caused by C1-inhibitor deficiency, not vasoocclusion.

Educational objective:
Dactylitis (painful swelling of the hands and feet) is a common presentation of sickle cell disease (SCD) in young children. It is one of many vasoocclusive manifestations of SCD. Sickling episodes result in hemolysis, which leads to increased indirect bilirubin and lactate dehydrogenase and decreased levels of haptoglobin.

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A 28-year-old woman comes to the emergency department with acute-onset abdominal pain, nausea, and confusion. She has no significant past medical history and does not use tobacco or alcohol as they have made her feel sick in the past. Serum lipase and liver function tests are within normal limits. CT scan of the abdomen shows no abnormalities. A sample of her urine is reddish in color and darkens on standing for 24 hours. Intravenous dextrose is administered and her symptoms improve significantly. Dextrose infusion most likely improved this patient's condition by affecting which of the following pathways?

A. Gluconeogenesis
B. Fatty acid synthesis
C. Ketone body formation
D. Porphyrin synthesis
E. Protein catabolism
F. Purine degradation

Submit

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A 28-year-old woman comes to the emergency department with acute-onset abdominal pain, nausea, and confusion. She has no significant past medical history and does not use tobacco or alcohol as they have made her feel sick in the past. Serum lipase and liver function tests are within normal limits. CT scan of the abdomen shows no abnormalities. A sample of her urine is reddish in color and darkens on standing for 24 hours. Intravenous dextrose is administered and her symptoms improve significantly. Dextrose infusion most likely improved this patient's condition by affecting which of the following pathways?

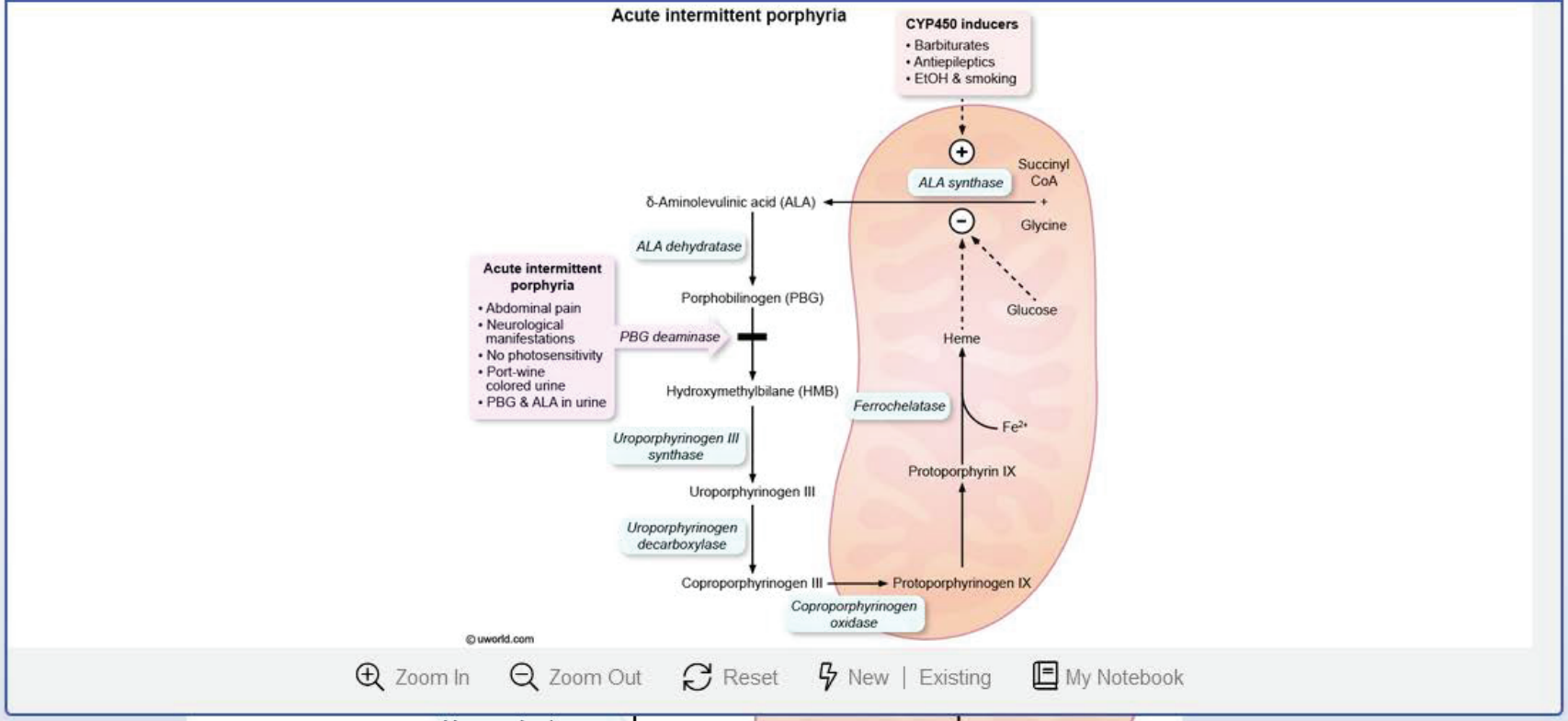
A. ~~Gluconeogenesis~~ (11%)
B. ~~Fatty acid synthesis~~ (2%)
C. ~~Ketone body formation~~ (8%)
✓ D. Porphyrin synthesis (61%)
E. Protein catabolism (11%)
F. Purine degradation (4%)

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CYP450 inducers

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This patient most likely has **acute intermittent porphyria (AIP)**, an autosomal dominant disorder of the heme synthesis pathway caused by **porphobilinogen (PBG) deaminase deficiency**. In general, enzyme deficiencies in the early steps of porphyrin synthesis cause neurovisceral symptoms (acute porphyrias); deficiencies in the latter steps (after condensation of PBG to HMB) result in photosensitivity (cutaneous porphyrias).

AIP is an acute porphyria that causes nervous system dysfunction due to the accumulation of early heme pathway intermediates (PBG and delta-aminolevulinic acid [ALA]). It presents **acutely** with variable **gastrointestinal and neurologic symptoms**, most commonly abdominal pain, vomiting, peripheral neuropathy, and neuropsychiatric derangements. A key feature of acute porphyrias is reddish urine that darkens on exposure to light and air due to the oxidation of excess PBG.

Treatment and prevention of acute porphyria attacks is directed at **inhibiting ALA synthase** (the rate-limiting enzyme of heme synthesis) to reduce formation of the toxic intermediate metabolites. ALA synthase is upregulated by **CYP450 inducers** (eg, most antiepileptics, griseofulvin, rifampin) and downregulated by **heme** and **glucose**. As such, avoidance of alcohol, smoking, and other CYP450-inducing drugs is important for preventing acute attacks. Likewise, intravenous heme administration and carbohydrate loading (such as with dextrose infusion) are useful for ameliorating acute symptoms

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downregulated by **heme** and **glucose**. As such, avoidance of alcohol, smoking, and other CYP450-inducing drugs is important for preventing acute attacks. Likewise, intravenous heme administration and carbohydrate loading (such as with dextrose infusion) are useful for ameliorating acute symptoms.

(Choices A, B, C, E, and F) Administration of intravenous dextrose inhibits peroxisome proliferator-activated receptor-gamma, a transcription factor that induces synthesis of ALA synthase. This improves the symptoms of AIP by reducing the overall activity of the porphyrin synthesis pathway.

Educational objective:

Acute intermittent porphyria is an autosomal dominant condition caused by porphobilinogen deaminase deficiency. Most patients remain asymptomatic, but a minority present with acute attacks characterized by abdominal pain and vomiting, peripheral neuropathy, neuropsychological symptoms, and reddish-brown urine. Treatment consists of intravenous glucose or heme preparations, which downregulate ALA synthase activity.

Pathophysiology	Hematology & Oncology	Acute intermittent porphyria
Subject	System	Topic

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A 3-year-old boy diagnosed with thalassemia major receives multiple transfusions to maintain his blood hemoglobin level. On physical examination, his liver and spleen are mildly enlarged. He also has glucose intolerance as demonstrated by an oral glucose tolerance test. Which of the following therapies would prevent congestive cardiac failure in this patient?

- A. Erythropoietin
- B. Cobalamin
- C. Deferoxamine
- D. Ascorbic acid
- E. Digoxin

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A 3-year-old boy diagnosed with thalassemia major receives multiple transfusions to maintain his blood hemoglobin level. On physical examination, his liver and spleen are mildly enlarged. He also has glucose intolerance as demonstrated by an oral glucose tolerance test. Which of the following therapies would prevent congestive cardiac failure in this patient?

- A. Erythropoietin (5%)
- B. Cobalamin (2%)
- ✓ C. Deferoxamine (82%)
- D. Ascorbic acid (2%)
- E. Digoxin (6%)

Correct

82%
Answered correctly

27 secs
Time Spent

09/25/2020
Last Updated

Explanation

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A. Erythropoietin (5%)
B. Cobalamin (2%)
C. Deferoxamine (82%)
D. Ascorbic acid (2%)
E. Digoxin (6%)

Correct

82%
Answered correctly

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Time Spent

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Explanation

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Many hemolytic diseases (eg, thalassemia major) require frequent, regular treatment with red blood cell transfusions for the maintenance of an adequate hemoglobin level. Over time, these **chronic red blood cell transfusions** cause **iron** to accumulate within the reticuloendothelial system and organs such as the liver and heart. Because iron **cardiotoxicity** may result in arrhythmias and congestive heart failure, it is important to implement chelation therapy within one to two years of beginning red blood cell transfusions.

Chelation therapy allows for the removal of excessive iron from the body, and can delay or prevent the development of cardiac disease. **Deferoxamine** is one of the more effective and safe iron chelators, as it complexes with ferric ions to form ferrioxamine, which is removed by the kidneys.

(Choices A, B, D, and E) Erythropoietin induces erythropoiesis and reticulocyte release from the bone marrow. It is commonly used to treat the anemia of chronic kidney disease. Cobalamin (vitamin B_{12}) is necessary in the treatment of pernicious anemia. Ascorbic acid (vitamin C) is used in the treatment of scurvy. Digoxin causes increased cardiac contractility, enhanced vagal tone, and decreased ventricular rate. As such, it is used in the treatment of congestive heart failure and supraventricular arrhythmias.

None of these therapies are capable of preventing congestive heart failure secondary to iron cardiotoxicity, however.

Educational objective:

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None of these therapies are capable of preventing congestive heart failure secondary to iron cardiotoxicity, however.

Educational objective:
Chelation therapy with deferoxamine should be implemented in patients receiving chronic red blood cell transfusions. Deferoxamine prevents iron-induced cardiotoxicity and congestive heart failure from developing in this patient population.

Pathology	Hematology & Oncology	Iron poisoning
Subject	System	Topic

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A 20-year-old woman comes to the emergency department due to bloody stools. Approximately an hour ago, the patient had a bowel movement that appeared grossly bloody. For the past month, she has also had decreased energy. Temperature is 37 C (98.6 F), blood pressure is 110/60 mm Hg, pulse is 110/min, and respirations are 20/min. The patient appears tired. Cardiopulmonary examination reveals mild tachycardia. The abdomen is soft without organomegaly. Skin examination shows pallor and scattered bruises in various stages of healing throughout the trunk. Complete blood count results are as follows:

Hemoglobin	7.2 g/dL
Mean corpuscular volume	90 μm^3
Platelets	10,000/mm^3
Leukocytes	1,050/mm^3
Neutrophils	5%
Lymphocytes	95%

Which of the following is the most likely cause of this patient's condition?

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Platelets	10,000/mm^3
Leukocytes	1,050/mm^3
Neutrophils	5%
Lymphocytes	95%

Which of the following is the most likely cause of this patient's condition?

A. Autoimmune-induced loss of self-renewing hematopoietic stem cells

B. Bone marrow replacement by constitutively active tyrosine kinase–stimulated cells

C. Splenic hyperactivity with cell trapping by the reticuloendothelial system

D. Increased destruction of cells opsonized by glycoprotein IIb/IIIa-targeted autoantibodies

E. Ineffective hematopoiesis secondary to micronutrient deficiency

Submit

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Mean corpuscular volume	90 µm³
Platelets	10,000/mm³
Leukocytes	1,050/mm³
Neutrophils	5%
Lymphocytes	95%

Which of the following is the most likely cause of this patient's condition?

A. Autoimmune-induced loss of self-renewing hematopoietic stem cells (45%)

B. Bone marrow replacement by constitutively active tyrosine kinase–stimulated cells (27%)

C. ~~Splenic hyperactivity with cell trapping by the reticuloendothelial system~~ (5%)

D. ~~Increased destruction of cells opsonized by glycoprotein IIb/IIIa-targeted autoantibodies~~ (15%)

E. ~~Ineffective hematopoiesis secondary to micronutrient deficiency~~ (5%)

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Causes of pancytopenia	
Bone marrow aplasia	• Aplastic anemia • Infection (eg, parvovirus, HIV, viral hepatitis) • Nutritional deficiency (eg, vitamin B_{12}/folate) • Medications (eg, hydroxyurea)
Bone marrow infiltration	• Cancer (eg, hematologic, metastatic) • Myelofibrosis • Infection (eg, tuberculosis, fungal infection)
Mature blood cell destruction	• Intravascular (eg, DIC, TTP) • Extravascular (eg, hypersplenism)

DIC = disseminated intravascular coagulation; **TTP** = thrombotic thrombocytopenic purpura.

This patient has gastrointestinal bleeding and ecchymosis secondary to thrombocytopenia; although anemia (eg, pallor) would be expected with significant bleeding, her low leukocyte count indicates **pancytopenia**, which is generally caused by one of the following:

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	• Extravascular (eg, hypersplenism)

DIC = disseminated intravascular coagulation; **TTP** = thrombotic thrombocytopenic purpura.

This patient has gastrointestinal bleeding and ecchymosis secondary to thrombocytopenia; although anemia (eg, pallor) would be expected with significant bleeding, her low leukocyte count indicates **pancytopenia**, which is generally caused by one of the following:

- **Bone marrow aplasia:** Hematopoietic stem cells in the bone marrow are unable to proliferate and differentiate into mature blood cells due to aplastic anemia, nutritional impairment, infection (eg, parvovirus, HIV), or cytotoxic medications.
- **Bone marrow infiltration:** Cancer, fibrosis, or infection (eg, tuberculosis) fills the bone marrow and crowds out hematologic cells, thereby preventing blood cell replication and maturation.
- **Mature blood cell destruction:** Circulating mature blood cells may be destroyed due to disseminated intravascular coagulation or thrombotic thrombocytopenic purpura; extravascular mature blood cells may be destroyed or sequestered in the spleen due to hypersplenism.

Based on this patient's laboratory and physical examination results, several answer choices can be eliminated. The presence of a normal MCV makes vitamin B_{12} or folate deficiency unlikely because these are associated with macrocytic (not normocytic) anemia **(Choice E)**. Hypersplenism is also unlikely

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Based on this patient's laboratory and physical examination results, several answer choices can be eliminated. The presence of a normal MCV makes vitamin B_{12} or folate deficiency unlikely because these are associated with macrocytic (not normocytic) anemia **(Choice E)**. Hypersplenism is also unlikely because abdominal examination would show significant splenomegaly **(Choice C)**. Chronic myelogenous leukemia, an infiltrative cancer associated with constitutively active tyrosine kinase, is also unlikely because this condition is usually associated with dramatic leukocytosis (not leukopenia) **(Choice B)**.

Therefore, the most likely cause of this patient's pancytopenia is **aplastic anemia** (AA). Although AA is linked to certain medications, infections, toxins, or radiation, most cases are **idiopathic** and thought to be caused by **autoimmune-induced loss of multipotent hematologic stem cells**. In idiopathic AA, an underlying insult (eg, mutation, virus) causes alteration of surface antigens on multipotent stem cells, making them appear foreign and triggering a **cytotoxic T-cell response**. Cytokines released by T-helper cells (type 1 cytokines) also contribute to the pathogenesis, most notably **interferon-gamma**, which triggers **apoptotic cell death** due to the stimulation of a destructive cytokine cascade and the increased expression of the Fas receptor on the hematologic stem cell surface.

(Choice D) Autoantibodies against glycoprotein IIb/IIIa cause immune thrombocytopenia, which is marked by thrombocytopenia and no change in the other cell lines.

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underlying insult (eg, mutation, virus) causes alteration of surface antigens on multipotent stem cells, making them appear foreign and triggering a **cytotoxic T-cell response**. Cytokines released by T-helper cells (type 1 cytokines) also contribute to the pathogenesis, most notably **interferon-gamma**, which triggers **apoptotic cell death** due to the stimulation of a destructive cytokine cascade and the increased expression of the Fas receptor on the hematologic stem cell surface.

(Choice D) Autoantibodies against glycoprotein IIb/IIIa cause immune thrombocytopenia, which is marked by thrombocytopenia and no change in the other cell lines.

Educational objective:

Aplastic anemia is a form of bone marrow failure in which patients have decreased production of all cell lines (platelets, erythrocytes, and leukocytes). It is primarily caused by the autoimmune destruction of multipotent hematologic stem cells due to an alteration in their surface antigens, leading to a cytotoxic T-cell response and release of interferon-gamma from T-helper cells (triggers apoptotic cell death).

Pathology	Hematology & Oncology	Aplastic anemia
Subject	System	Topic

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A 64-year-old man is evaluated for a 1-month history of worsening fatigue and low back pain exacerbated by movement. He has no prior medical history and takes no medications. Vital signs are normal. Physical examination shows mucosal pallor and bony tenderness. Radiographs reveal lytic bone lesions. Laboratory studies show that hemoglobin is 8.8 g/dL, serum creatinine is 3.0 g/dL, and serum calcium is 10.8 g/dL. Urine dipstick is negative for protein, but quantitative measurement reveals elevated 24-hour urinary protein excretion. Urine electrophoresis is most likely to detect which of the following?

A. Gamma heavy chains
B. Immunoglobulin A
C. Immunoglobulin G
D. Immunoglobulin M
E. Lambda light chains

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A. Gamma heavy chains (8%)
B. Immunoglobulin A (1%)
C. Immunoglobulin G (19%)
D. Immunoglobulin M (13%)
E. Lambda light chains (58%)

Correct

58% Answered correctly

34 secs Time Spent

11/29/2020 Last Updated

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Multiple myeloma (MM) is a lymphoproliferative malignancy characterized by monoclonal plasma cell proliferation and production of monoclonal paraproteins (eg, immunoglobulins, chain fragments). MM should be suspected in elderly patients who have any combination of osteolytic lesions, hypercalcemia, anemia, or acute kidney injury (such as this patient). Other common symptoms include weight loss, constipation (due to hypercalcemia), fatigue, and recurrent infection.

Kidney disease in MM is largely due to **light chain cast nephropathy** (myeloma kidney). Intact immunoglobulins (eg, IgA, IgG, IgM) are too large to pass through the glomerulus, but a small amount of free light chains (eg, kappa, lambda) are freely filtered and resorbed in the proximal tubules. However in MM, the excessive quantities of free light chains exceed the resorptive capacity of the kidney. The filtered light chains then combine with Tamm-Horsfall proteins to form **obstructive casts** that cause tubular rupture and kidney injury.

Monoclonal paraproteins are **not detected by urine dipstick** (which detects only albumin), but **quantitative protein concentrations** (spot or 24-hour turbidimetric assay) will be elevated. Urine protein electrophoresis, immunofixation, or free light chain immunoassays can be used for diagnosis.

(Choices A, B, C, and D) MM can occasionally cause monoclonal immunoglobulin deposition disease, in which intact immunoglobulins or heavy and/or light chains deposit on the kidney basement membranes,

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quantitative protein concentrations (spot or 24-hour turbidimetric assay) will be elevated. Urine protein electrophoresis, immunofixation, or free light chain immunoassays can be used for diagnosis.

(Choices A, B, C, and D) MM can occasionally cause monoclonal immunoglobulin deposition disease, in which intact immunoglobulins or heavy and/or light chains deposit on the kidney basement membranes, resulting in glomerular disease and nephrotic syndrome. In this case, large intact immunoglobulins (and heavy chains) can enter the urine; however, albumin (which also passes through the injured glomerulus) would be detected on urine dipstick.

Educational objective:
Multiple myeloma should be suspected in elderly patients who have any combination of osteolytic lesions, hypercalcemia, anemia, or acute kidney injury. Renal disease is most commonly caused by light chain cast nephropathy, in which free light chains form obstructive casts in the renal tubules. Monoclonal paraproteins are not detected by urine dipstick (which detects only albumin), but both spot and 24-hour protein concentrations will be elevated.

Pathophysiology	Hematology & Oncology	Multiple myeloma
Subject	System	Topic

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A 35-year-old woman comes to the office for evaluation of fatigue and exertional dyspnea. She has a history of systemic lupus erythematosus and is noncompliant with therapy. The patient takes naproxen as needed for joint pains. Vital signs are within normal limits. Examination shows mild pallor. The remainder of the examination shows no abnormalities. Laboratory results are as follows:

Hemoglobin	8.6 g/dL	
Mean corpuscular volume	80 mm^3	
Creatinine	0.8 mg/dL	
Iron, serum	40 µg/dL	
Total iron-binding capacity	180 µg/dL	(normal: 250-460 µg/dL)
Lactate dehydrogenase	72 U/L	

Which of the following is the most likely underlying cause of her current condition?

A. Immune hemolysis of erythrocytes

B. Increased cellular use of folic acid

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Mean corpuscular volume	80 mm^3	
Creatinine	0.8 mg/dL	
Iron, serum	40 µg/dL	
Total iron-binding capacity	180 µg/dL	(normal: 250-460 µg/dL)
Lactate dehydrogenase	72 U/L	

Which of the following is the most likely underlying cause of her current condition?

A. Immune hemolysis of erythrocytes
B. Increased cellular use of folic acid
C. Intrinsic factor antibodies
D. Iron sequestration in macrophages
E. Occult gastrointestinal blood loss

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Mean corpuscular volume	80 mm^3	
Creatinine	0.8 mg/dL	
Iron, serum	40 µg/dL	
Total iron-binding capacity	180 µg/dL	(normal: 250-460 µg/dL)
Lactate dehydrogenase	72 U/L	

Which of the following is the most likely underlying cause of her current condition?

A. ~~Immune hemolysis of erythrocytes~~ (17%)

B. ~~Increased cellular use of folic acid~~ (0%)

C. ~~Intrinsic factor antibodies~~ (1%)

✓ D. Iron sequestration in macrophages (70%)

E. Occult gastrointestinal blood loss (10%)

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	Iron deficiency anemia	Anemia of chronic disease
Serum ferritin	↓	Normal or ↑
Serum iron	↓	↓
Mean corpuscular volume	↓	Normal or ↓
Transferrin (total iron-binding capacity)	↑	Normal or ↓
Transferrin saturation	↓	↓
Erythropoietin	↑	Variable*
Hepcidin	↓	↑
C-reactive protein	Normal	↑

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C-reactive protein	Normal	↑
Serum cytokines	Normal	↑

* Lower than expected for the degree of anemia.

This patient with untreated systemic lupus erythematosus (SLE) has normocytic anemia with low serum iron and low total iron-binding capacity, raising strong suspicion for **anemia of chronic disease** (ACD). Most cases arise in those with **chronic elevation of inflammatory cytokines** due to underlying rheumatologic disease (eg, SLE), chronic infection, or malignancy. Although a number of inflammatory cytokines contribute to the development of ACD, the primary mediator is **hepcidin**, a small peptide released by the liver in response to inflammation.

Hepcidin binds to and inactivates iron channels (ferroportin) on enterocytes and reticuloendothelial macrophages, which results in reduced iron absorption in the gut and **increased iron sequestration** in the reticuloendothelial system. Because **reticuloendothelial macrophages** recycle senescent erythrocytes and provide >95% of daily iron for erythrocytosis, sequestration of iron in the reticuloendothelial system dramatically **reduces serum iron concentration**. This limits the amount of iron available for the generation of new erythrocytes and typically results in a normocytic (or slightly microcytic) anemia with a low reticulocyte response. In ACD, **total iron-binding capacity** is generally **normal or slightly reduced**

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low reticulocyte response. In ACD, **total iron-binding capacity** is generally **normal or slightly reduced** due to cytokine-mediated suppression of transferrin.

(Choices A and E) Patients with SLE can develop immune-mediated hemolysis due to the generation of autoantibodies against the erythrocyte membrane; however, this typically results in extravascular hemolysis, which increases the intracellular enzyme lactate dehydrogenase. The presence of *normal lactate dehydrogenase* in this case makes hemolysis less likely. Patients with SLE also sometimes develop gastrointestinal bleeding from serositis (or chronic NSAID use), which can lead to iron deficiency anemia. However, iron deficiency anemia is typically associated with *microcytic anemia* and a *high total iron-binding capacity* (because transferrin levels are markedly increased).

(Choices B and C) Conditions associated with rapid cell turnover can result in folate deficiency due to increased folate use during the generation of new cells. Intrinsic factor antibodies are a common cause of vitamin B_{12} deficiency. However, folate and vitamin B_{12} deficiency are generally marked by macrocytic anemia with a normal or *high serum iron level*.

Educational objective:
Anemia of chronic disease is a consequence of chronically elevated inflammatory cytokines, most importantly hepcidin. This peptide inactivates iron channels on enterocytes and reticuloendothelial

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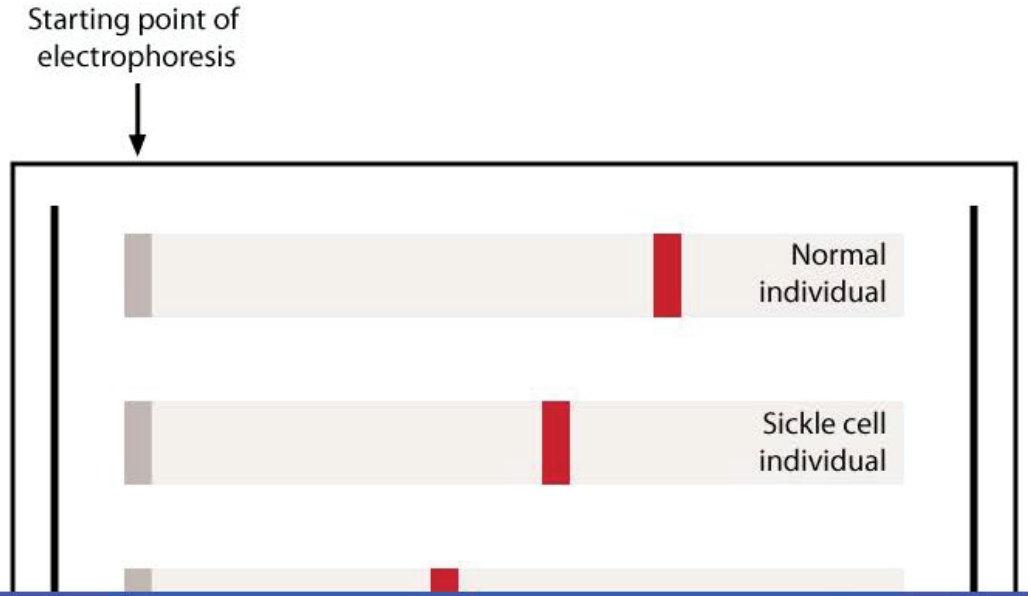
hemolysis, which increases the intracellular enzyme lactate dehydrogenase. The presence of *normal lactate dehydrogenase* in this case makes hemolysis less likely. Patients with SLE also sometimes develop gastrointestinal bleeding from serositis (or chronic NSAID use), which can lead to iron deficiency anemia. However, iron deficiency anemia is typically associated with *microcytic anemia* and a *high total iron-binding capacity* (because transferrin levels are markedly increased).

(Choices B and C) Conditions associated with rapid cell turnover can result in folate deficiency due to increased folate use during the generation of new cells. Intrinsic factor antibodies are a common cause of vitamin B_{12} deficiency. However, folate and vitamin B_{12} deficiency are generally marked by macrocytic anemia with a normal or *high serum iron level*.

Educational objective:
Anemia of chronic disease is a consequence of chronically elevated inflammatory cytokines, most importantly hepcidin. This peptide inactivates iron channels on enterocytes and reticuloendothelial macrophages, leading to reduced iron absorption and reduced iron release from the reticuloendothelial system. The net result is normocytic or slightly microcytic anemia with low reticulocyte response, low serum iron level, and normal or low total iron-binding capacity.

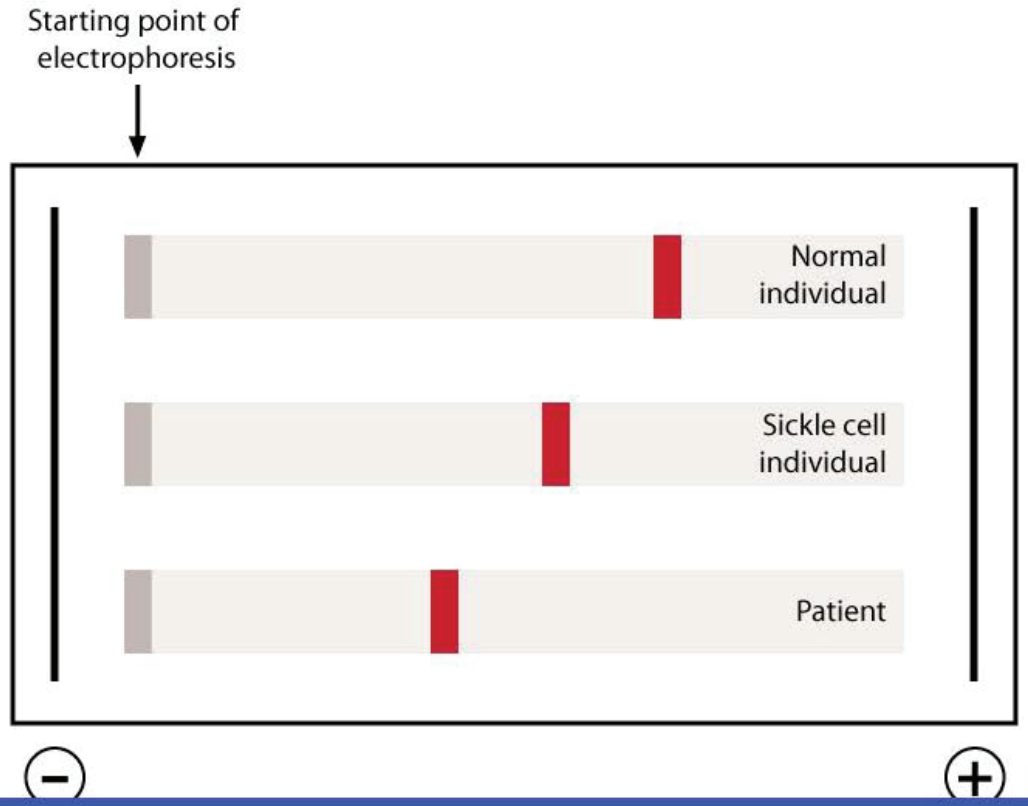
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A 6-year-old African American boy is brought to the physician because of easy fatigability. Physical examination reveals splenomegaly, and his complete blood count shows mild anemia. Hemoglobin electrophoresis is performed at alkaline pH on a cellulose acetate strip. Findings for the patient are shown below compared to individuals with normal hemoglobin and known sickle cell disease.



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below compared to individuals with normal hemoglobin and known sickle cell disease.



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Which of the following is the most likely cause of this patient's condition?

A. Alpha globin gene deletion
B. Missense mutation
C. Nonsense mutation
D. Silent mutation
E. Trinucleotide expansion

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Which of the following is the most likely cause of this patient's condition?

- A. ~~Alpha globin gene deletion~~ (23%)
- ✓ B. Missense mutation (55%)
- C. Nonsense mutation (14%)
- D. ~~Silent mutation~~ (0%)
- E. ~~Trinucleotide expansion~~ (6%)

Correct

55%

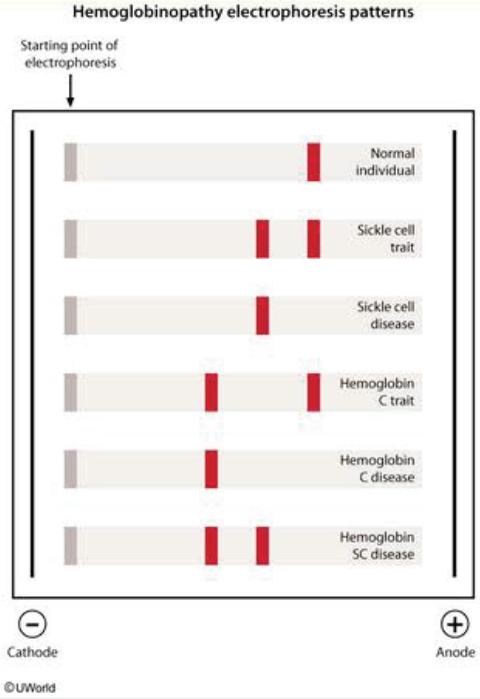
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Hemoglobin electrophoresis is used to assess for different forms of hemoglobin in patients with suspected hemoglobinopathy. Normal hemoglobin consists primarily of **hemoglobin A** (HbA), which **migrates rapidly** toward the positive electrode (anode) because of its negative charge. Hemoglobin S (HbS) is an abnormal type of hemoglobin in which a nonpolar amino acid (valine) replaces a negatively charged amino acid (glutamate) in the beta globin chain. This amino acid replacement decreases the negative charge on the HbS molecule, which causes **HbS** to move more **slowly** toward the anode. Similarly, hemoglobin C (HbC) has a glutamate residue replaced by lysine in the beta globin chain. Because lysine is a positively charged amino acid, **HbC** has even less total negative charge than HbS and moves **even more slowly** toward the anode. Both HbC and HbS result from **missense mutations**, a type of mutation in which a single base substitution results in a codon that codes for a different amino acid.

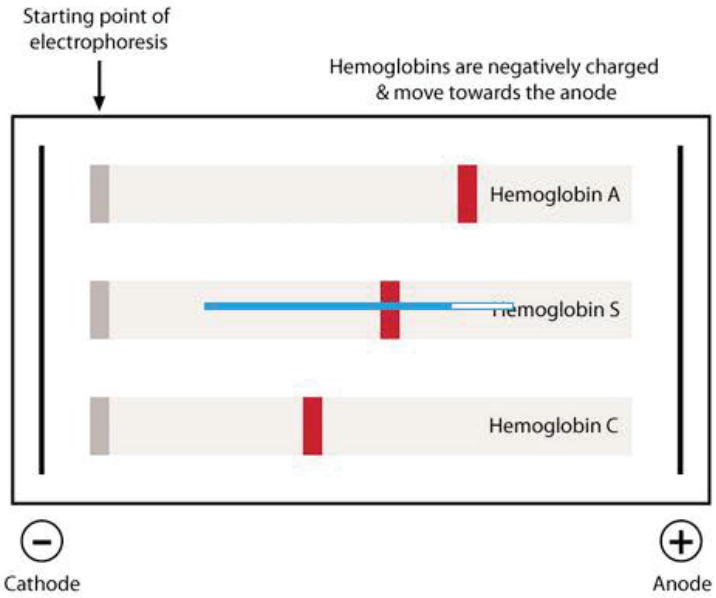
Patients with sickle cell disease have HbS mutations in both beta chains; those with HbC disease have HbC mutations involving both beta chains. Patients with hemoglobin SC disease have 1 HbS allele and 1 HbC allele and will have 2 hemoglobin bands on electrophoresis. This patient's electrophoresis results show a **single band** that **migrates less than the HbA and HbS** bands, meaning that he has **HbC disease**. Patients with HbC disease are typically asymptomatic and often have mild hemolytic anemia and splenomegaly.

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Hemoglobin electrophoresis



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splenomegaly.

(Choice A) Deletions involving the alpha globin genes cause alpha thalassemia, which results in imbalanced beta chain production and formation of beta tetramers (hemoglobin H) that migrate further than HbA during electrophoresis.

(Choice C) Nonsense mutations introduce a stop codon within gene sequences, resulting in the formation of truncated proteins. As a result of their decreased size, these proteins tend to move further during electrophoresis.

(Choice D) Silent mutations are point mutations that have no effect on the protein formed. A mutation from UCA to UCC does not result in any change in protein structure as both codons result in the placement of serine into the growing polypeptide chain.

(Choice E) Trinucleotide expansions increase the number of trinucleotide repeats within a gene, resulting in large, unstable proteins or alterations in the epigenetic effects. These proteins would tend to move less during electrophoresis due to their increased size. However, the hemoglobinopathies are not caused by trinucleotide expansions, as the hemoglobin genes do not contain trinucleotide repeat regions.

Educational objective:
Hemoglobin C is caused by a missense mutation that results in a glutamate residue being substituted by

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electrophoresis.

(Choice D) Silent mutations are point mutations that have no effect on the protein formed. A mutation from UCA to UCC does not result in any change in protein structure as both codons result in the placement of serine into the growing polypeptide chain.

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Educational objective:
Hemoglobin C is caused by a missense mutation that results in a glutamate residue being substituted by lysine in the beta globin chain. This results in an overall decrease in negative charge for the hemoglobin molecule. The speed of hemoglobin movement during gel electrophoresis is hemoglobin A > hemoglobin S > hemoglobin C.

Biochemistry	Hematology & Oncology	Hemoglobin c disease
Subject	System	Topic

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Two antineoplastic drugs are shown to inhibit intracellular thymidylate formation. The chemotherapeutic effect of drug X can be overcome by N^5-formyl-tetrahydrofolate supplementation, but that of drug Y is not affected. The drugs described in this scenario are most likely which of the following?

	Drug X	Drug Y
A.	Cytarabine	Gemcitabine
B.	Fluorouracil	Leucovorin
C.	Fludarabine	Methotrexate
D.	Methotrexate	Fluorouracil
E.	Gemcitabine	Fludarabine

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Two antineoplastic drugs are shown to inhibit intracellular thymidylate formation. The chemotherapeutic effect of drug X can be overcome by N^5-formyl-tetrahydrofolate supplementation, but that of drug Y is not affected. The drugs described in this scenario are most likely which of the following?

	Drug X	Drug Y	
A.	Cytarabine	Gemcitabine	(1%)
B.	Fluorouracil	Leucovorin	(7%)
C.	Fludarabine	Methotrexate	(4%)
✓ D.	Methotrexate	Fluorouracil	(85%)
E.	Gemcitabine	Fludarabine	(0%)

Correct

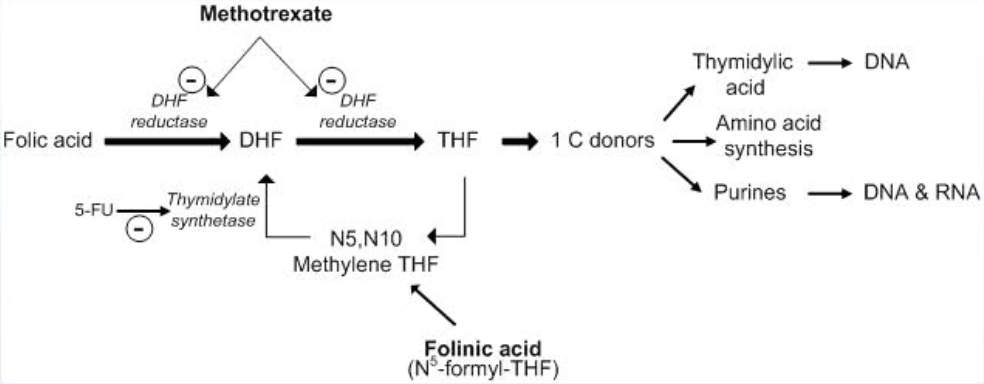
85% Answered correctly

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Explanation



The two antineoplastic agents described in the question stem are methotrexate (Drug X) and 5-fluorouracil (Drug Y). Methotrexate is a folic acid analog that functions by binding and inactivating dihydrofolate reductase, the enzyme responsible for reducing folic acid to tetrahydrofolate. Tetrahydrofolate participates in the transfer of carbon groups in certain intracellular reactions including purine and thymidine synthesis. 5-fluorouracil (5-FU) is a pyrimidine analog that primarily functions to inhibit DNA synthesis by inhibition of thymidylate synthetase after enzymatic conversion to its nucleotide floxuridine monophosphate by any of a

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(N⁵-formyl-THF)

The two antineoplastic agents described in the question stem are methotrexate (Drug X) and 5-fluorouracil (Drug Y). Methotrexate is a folic acid analog that functions by binding and inactivating dihydrofolate reductase, the enzyme responsible for reducing folic acid to tetrahydrofolate. Tetrahydrofolate participates in the transfer of carbon groups in certain intracellular reactions including purine and thymidine synthesis. 5-fluorouracil (5-FU) is a pyrimidine analog that primarily functions to inhibit DNA synthesis by inhibition of thymidylate synthetase after enzymatic conversion to its nucleotide floxuridine monophosphate by any of a number of intracellular reactions.

The key metabolic difference between methotrexate and 5-fluorouracil is that methotrexate prevents the reduction of folic acid to tetrahydrofolate, while 5-FU binds tetrahydrofolate and thymidylate synthetase in a stable-reaction intermediate form, thereby effectively decreasing the amount of thymidylate synthetase available for thymidine synthesis.

Leucovorin (N^5-formyl-tetrahydrofolate) is a tetrahydrofolate derivative that does not require reduction by dihydrofolate reductase before it can function as a cofactor for thymidylate synthase and other enzymes involved with purine and amino acid synthesis. Because leucovorin bypasses the dihydrofolate reductase step that is inhibited by methotrexate, it can be used to "rescue" normal cells from the toxicity of methotrexate. 5-FU, on the other hand, requires the presence of reduced folate in order to form complexes

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methotrexate. 5-FU, on the other hand, requires the presence of reduced folate in order to form complexes with thymidylate synthetase. 5-FU has a reduced cytotoxic effect in cells that are deficient in tetrahydrofolate. For this reason, leucovorin can be utilized to potentiate the toxicity of fluoropyrimidines such as fluorouracil by strengthening the association of the drug with thymidylate synthase.

(Choice A) Cytarabine, like 5-FU, is also a pyrimidine analog antimetabolite that is incorporated into DNA leading to strand termination. It does not affect folate metabolism. Gemcitabine is another pyrimidine analog that functions much like cytarabine. It differs from cytarabine in that it is not S-phase specific, likely owing to additional cytotoxic functions such as inhibition of ribonucleotide reductase.

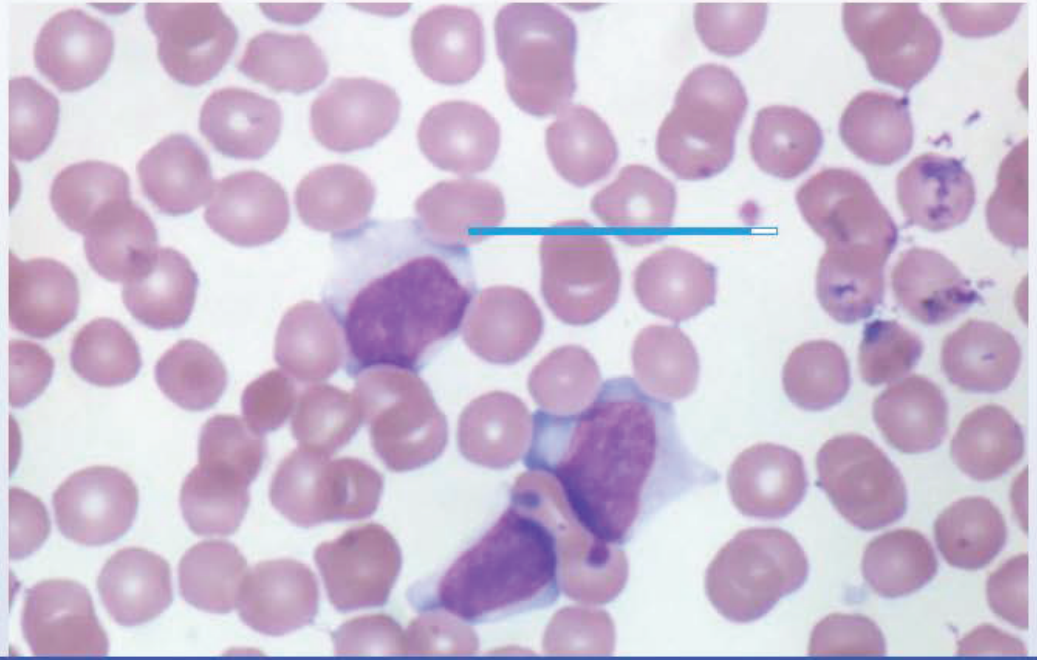
(Choice C) Fludarabine is a deamination-resistant purine nucleotide analog that exerts its cytotoxicity by many mechanisms, including inhibition of DNA polymerase, DNA primase, DNA ligase, and ribonucleotide reductase. Fludarabine is used to treat chronic lymphocytic leukemia (CLL).

Educational Objective:
Methotrexate and 5-FU both effectively inhibit thymidylate formation, but the chemotherapeutic effect of methotrexate is overcome by N^5-formyl-tetrahydrofolate (folinic acid, leucovorin) supplementation.

Pharmacology	Hematology & Oncology	Chemotherapy
Subject	System	Topic

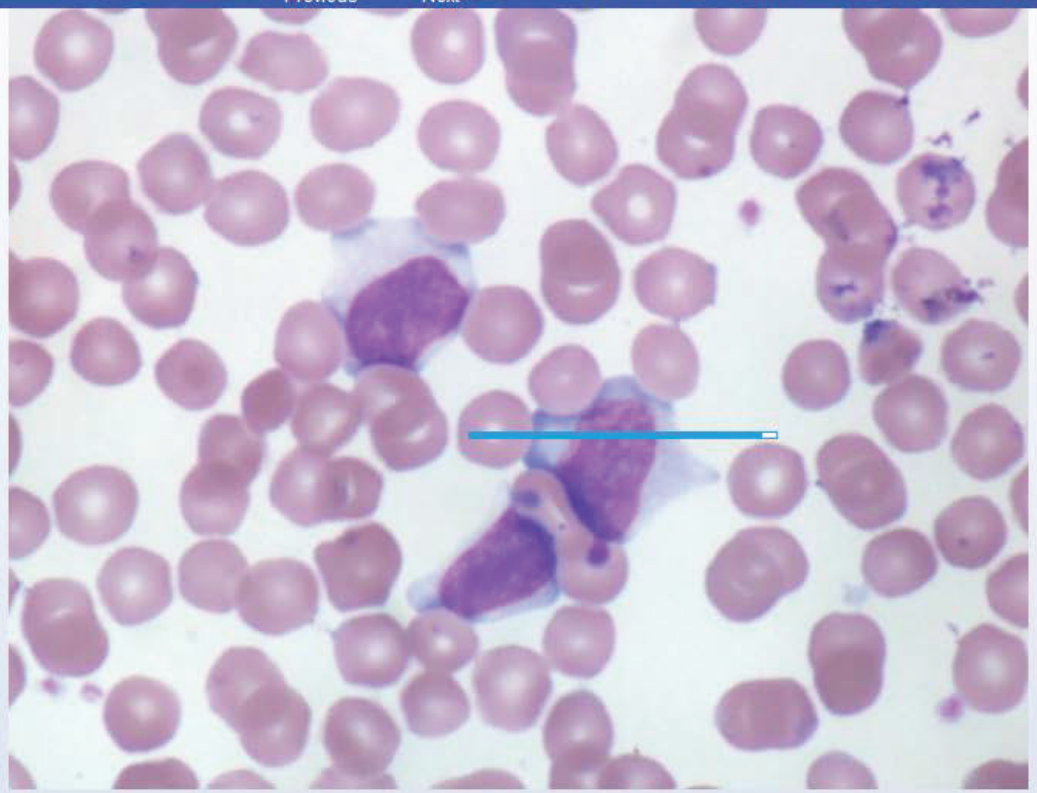
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A 15-year-old girl is evaluated due to persistent fever, fatigue, and sore throat. Physical examination reveals splenomegaly and symmetric posterior cervical lymphadenopathy. Peripheral blood smear results are shown in the image below:



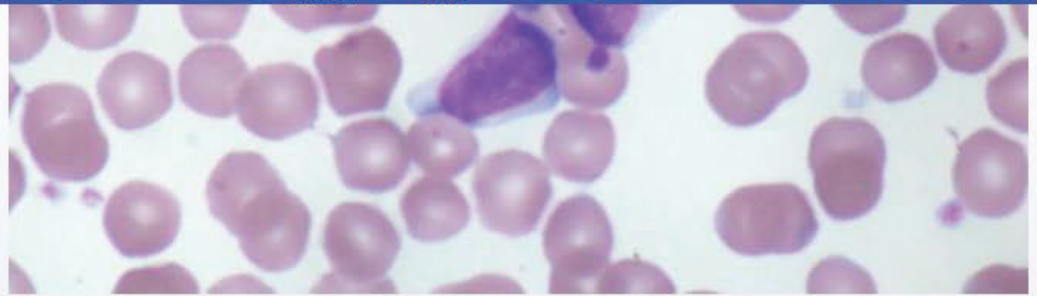
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The atypical cells seen here are most likely an activated form of which of the following?

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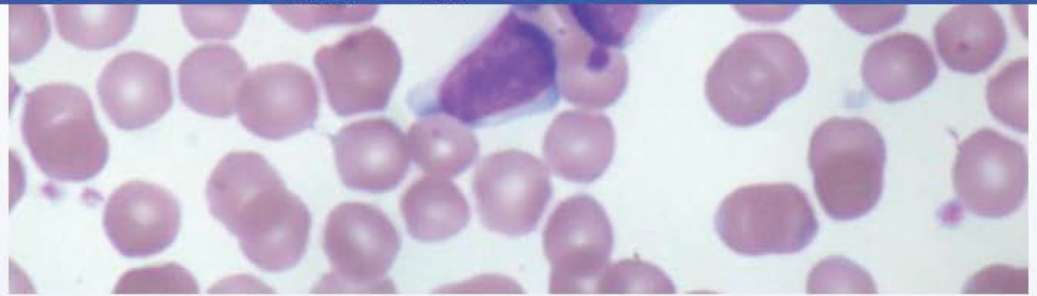


The atypical cells seen here are most likely an activated form of which of the following?

A. $CD4^+$ Helper lymphocytes
B. $CD8^+$ Cytotoxic lymphocytes
C. $CD14^+$ Monocytes
D. $CD21^+$ Lymphocytes
E. $CD27^+$ Plasma cells

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The atypical cells seen here are most likely an activated form of which of the following?

A. $CD4^+$ Helper lymphocytes (9%)

✓ B. $CD8^+$ Cytotoxic lymphocytes (52%)

C. ~~$CD14^-$ Monocytes~~ (7%)

✗ D. $CD21^+$ Lymphocytes (27%)

E. ~~$CD27^-$ Plasma cells~~ (3%)

Incorrect
Correct answer

52%

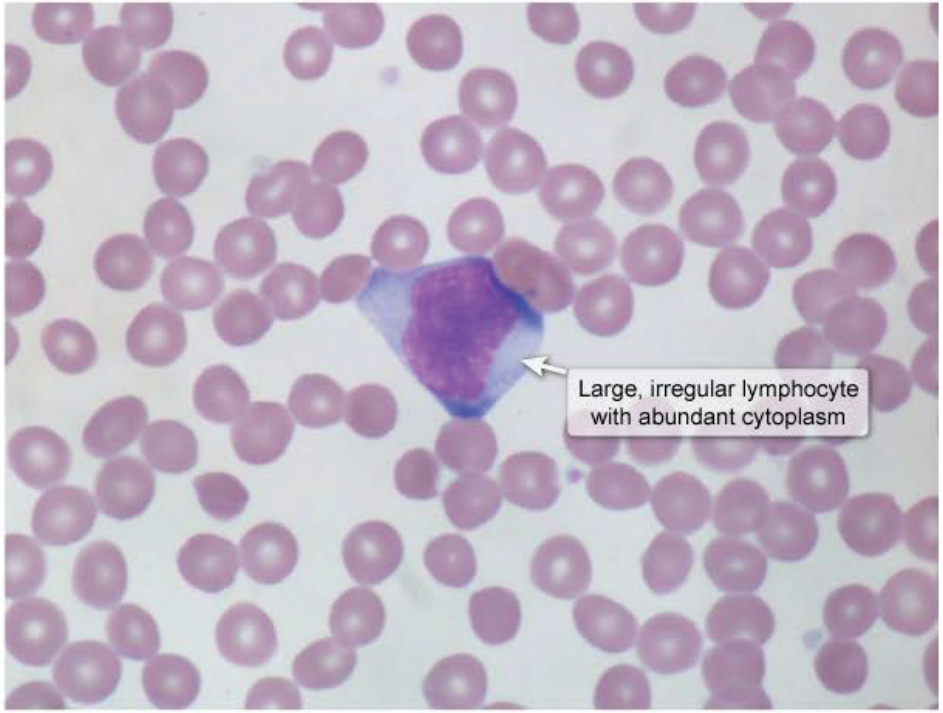
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Atypical CD8+ T lymphocyte



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This patient has fever, fatigue, sore throat, splenomegaly, symmetric posterior cervical lymphadenopathy, and atypical lymphocytosis characteristic of **infectious mononucleosis** (IM). After entering the bloodstream through the pharyngeal mucosa and tonsillar crypts, the **Epstein-Barr virus** (EBV) preferentially infects B lymphocytes by binding to CD21 cell surface receptors. EBV-infected B lymphocytes then activate **cytotoxic T lymphocytes ($CD8^+$)** through the presentation of viral antigens on major histocompatibility complex class I molecules. These reactive (atypical) $CD8^+$ T lymphocytes are the primary immune response to EBV and clonally expand to destroy virus-infected cells.

Atypical lymphocytes make up more than 10% of the cells in a peripheral blood smear in IM, and most (>95%) of those cells are $CD8^+$ T lymphocytes. They classically appear as **irregular cells** much larger than quiescent lymphocytes, with abundant basophilic cytoplasm and a cell membrane that appears to conform to the borders of neighboring cells. Although activated $CD21^+$ B lymphocytes and $CD4^+$ helper T lymphocytes can have a similar appearance in response to EBV infection, they make up <5% of the atypical lymphocytes in the peripheral circulation **(Choices A and D)**.

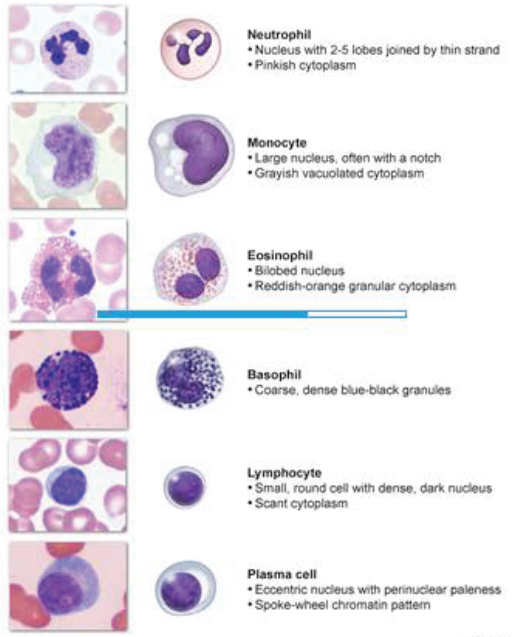
(Choice C) Monocytosis (eg, juvenile myelomonocytic leukemia) can be associated with persistent fever, fatigue, and splenomegaly; however, peripheral blood smear would show proliferation of blasts and dysplastic monocytes rather than atypical lymphocytes.

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Leukocytes in peripheral blood



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dysplastic monocytes rather than atypical lymphocytes

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(Choice C) Monocytosis (eg, juvenile myelomonocytic leukemia) can be associated with persistent fever, fatigue, and splenomegaly; however, peripheral blood smear would show proliferation of blasts and dysplastic monocytes rather than atypical lymphocytes.

(Choice E) Activated plasma cells appear on histology as ovoid cells with abundant cytoplasm and an eccentric nucleus with a spoke-wheel chromatin pattern. A zone of perinuclear clearing within the cytoplasm may also be noted, corresponding to the active Golgi body.

Educational objective:
The primary immune response to Epstein-Barr virus is mediated by CD8+ T lymphocytes, which are activated through the presentation of viral antigens on infected CD21+ B lymphocytes. These reactive (atypical) CD8+ T lymphocytes can be observed in the peripheral blood smears of patients with infectious mononucleosis.

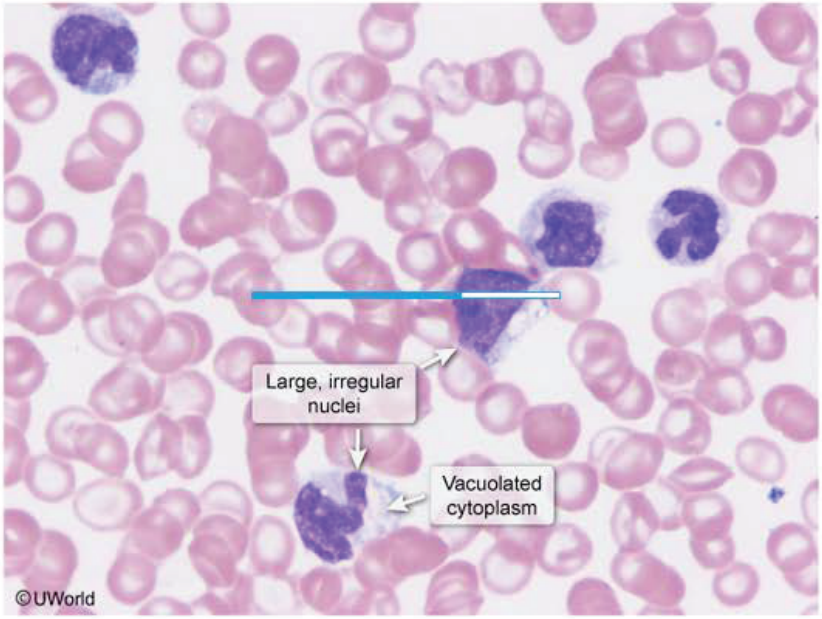
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Monocytosis



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Researchers studying chronic lymphocytic leukemia (CLL) observe that in some patients the disease is indolent, with limited growth over more than a decade, whereas in other patients the disease is more aggressive and becomes symptomatic early on. They find that genetic abnormalities can be detected in a majority of patients with CLL and may play a role in determining the difference between the 2 disease courses. A clinical study is conducted with the hypothesis that individuals with CLL with trisomy of chromosome 12 have a more favorable course than individuals with other genetic changes. Which of the following laboratory techniques would be most useful for identifying patients with this genetic abnormality?

A. Enzyme-linked immunosorbent assay
B. Flow cytometry
C. Fluorescence in situ hybridization
D. Northern blotting
E. Western blotting

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Researchers studying chronic lymphocytic leukemia (CLL) observe that in some patients the disease is indolent, with limited growth over more than a decade, whereas in other patients the disease is more aggressive and becomes symptomatic early on. They find that genetic abnormalities can be detected in a majority of patients with CLL and may play a role in determining the difference between the 2 disease courses. A clinical study is conducted with the hypothesis that individuals with CLL with trisomy of chromosome 12 have a more favorable course than individuals with other genetic changes. Which of the following laboratory techniques would be most useful for identifying patients with this genetic abnormality?

A. Enzyme-linked immunosorbent assay (2%)
B. Flow cytometry (6%)
✓ C. Fluorescence in situ hybridization (84%)
D. Northern blotting (4%)
E. Western blotting (2%)

84% 47 secs 01/30/2021

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Malignant cells typically contain a number of chromosomal translocations, deletions, or duplications that result in deregulation of gene expression and production of novel fusion proteins. **Cytogenic analysis** of tumor cells often demonstrates characteristic chromosomal abnormalities that may aid diagnosis, treatment selection, and estimation of prognosis.

Fluorescence in situ hybridization (FISH) is a highly sensitive cytogenetic test that can identify the presence of **chromosomal duplications** and **large deletions and translocations**. FISH probes are single-stranded DNA segments that are a few hundred kilobases in length; they are added to the cell of interest and anneal to complementary regions of the cell chromosome, which allows the area of interest to be identified visually.

FISH is far more sensitive than traditional karyotyping (chromosome banding) and can be applied to both dividing (metaphase) and nondividing (interphase) cells. It is often used to identify large structural chromosomal abnormalities such as the *BCR-ABL1* fusion of t(9;22) in chronic myeloid leukemia. However, small chromosomal insertions and deletions cannot be identified by FISH (because the probe size is somewhat large), and chromosomal inversions will be missed because FISH can only identify the presence or absence of a chromosomal segment, not the order in which it is coded.

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(Choice A) Enzyme-linked immunosorbent assay (ELISA) is used to quantify antibodies or antigens in a fluid.

(Choice B) Flow cytometry is often used in the diagnosis of leukemia. However, this laser-based test evaluates surface markers (eg, CD5) on individual cells, not chromosomal duplications.

(Choice D) Northern blotting is a technique that size-fractionates RNA in a gel and then targets a specific mRNA sequence of interest. It can determine the quantity and size of a particular mRNA section.

(Choice E) Western blotting is a technique that size-fractionates proteins in a gel and then targets a specific protein using an antibody with a radiotracer/enzyme. It is often used to confirm a positive ELISA test in the setting of HIV or Lyme disease infection.

Educational objective:
Fluorescence in situ hybridization (FISH) can identify specific chromosomal translocations, duplications, or deletions using a single-stranded, complementary DNA segment that is tagged with a radiotracer. FISH is rapid, highly sensitive and specific, and can be used on tissues with low mitotic rates. However, the targeted chromosomal abnormality must be somewhat large in order to be identified.

Biochemistry Hematology & Oncology Laboratory techniques

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A 56-year-old Caucasian male with non-Hodgkin lymphoma is undergoing systemic chemotherapy. Vincristine is a part of the regimen, and you suspect accidental overdose of that agent. Which of the following would you most expect in this patient?

A. Finger numbness and tingling
B. Burning on urination and urgency
C. Leg swelling and orthopnea
D. Dry cough and exertional dyspnea
E. Tarry stool and fatigue
F. Abdominal pain and jaundice

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A 56-year-old Caucasian male with non-Hodgkin lymphoma is undergoing systemic chemotherapy. Vincristine is a part of the regimen, and you suspect accidental overdose of that agent. Which of the following would you most expect in this patient?

- A. Finger numbness and tingling (76%)
- B. Burning on urination and urgency (4%)
- C. Leg swelling and orthopnea (3%)
- D. Dry cough and exertional dyspnea (3%)
- E. Tarry stool and fatigue (3%)
- F. Abdominal pain and jaundice (7%)

Correct

76% Answered correctly

39 secs Time Spent

01/30/2021 Last Updated

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Vincristine causes neurotoxicity by interfering with microtubule formation in nerve axons. Patients with vincristine toxicity most commonly complain of peripheral neuropathy, and neurotoxicity is the dose-limiting side effect **(Choice A)**. All vinca alkaloids (vincristine, vinblastine) inhibit microtubule polymerization after binding to β-tubulin. Inhibition of microtubule formation prevents synthesis of the mitotic spindle in dividing cells. Without the mitotic spindle, replicated chromosomes are unable to align and segregate into their respective daughter cells during mitosis. This leads to failure of division and cell death. Vinca alkaloid agents are thus M-phase specific agents.

(Choice B) Burning on urination and urgency may be seen with cyclophosphamide- or ifosfamide-induced hemorrhagic cystitis.

(Choice C) Leg swelling and orthopnea are symptoms of congestive heart failure. Of the chemotherapeutic agents, doxorubicin, an anthracycline antibiotic and a chemotherapeutic intercalating agent, is most commonly associated CHF.

(Choice D) Dry cough and exertional dyspnea may be seen with bleomycin, which is classically associated with pulmonary toxicity. Bleomycin specifically causes a progressive pulmonary fibrosis that can lead to death in a minority of patients.

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(Choice C) Leg swelling and orthopnea are symptoms of congestive heart failure. Of the chemotherapeutic agents, doxorubicin, an anthracycline antibiotic and a chemotherapeutic intercalating agent, is most commonly associated CHF.

(Choice D) Dry cough and exertional dyspnea may be seen with bleomycin, which is classically associated with pulmonary toxicity. Bleomycin specifically causes a progressive pulmonary fibrosis that can lead to death in a minority of patients.

(Choice E) Tarry stool and fatigue may be seen with any chemotherapeutic agent that affects rapidly-dividing cells, but are most classically associated with alkylating agents. These agents cause death in both the rapidly-dividing tumor cells, and in other groups of cells that have a high turn-over rate, like hair, skin, and the mucosa of the GI system. Tarry stool, also called melena, is most commonly due to an upper GI bleed.

(Choice F) Abdominal pain and jaundice may be seen with mercaptopurine use. Mercaptopurine is an S-phase specific purine analogue that is associated with cholestasis and hepatitis in a fair proportion of patients. Chronic methotrexate ingestion, used in rheumatoid arthritis for anti-inflammatory purposes, is also associated with cirrhosis.

Educational Objective:

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Educational Objective:
Neurotoxicity is the dose-limiting side effect of vincristine therapy. This toxicity results from failure of microtubule polymerization in neuronal axons. Other notable adverse effects classically associated with chemotherapeutic agents include pulmonary fibrosis and flagellate skin discoloration with bleomycin use; congestive heart failure with doxorubicin; and hemorrhagic cystitis with cyclophosphamide.

Pharmacology	Hematology & Oncology	Chemotherapy
Subject	System	Topic

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A 23-year-old woman comes to the emergency department with vaginal bleeding and lower abdominal cramps. Her last menstrual period was 6 weeks ago, and a home pregnancy test was positive. She has no medical history and does not use tobacco or alcohol. Pelvic ultrasonography reveals a gestational sac in the left fallopian tube without evidence of rupture. A single dose of methotrexate is administered to treat her condition. Which of the following substances will most likely accumulate in embryonic tissues as a result of treatment?

A. Dihydrofolate polyglutamate
B. Folinic acid
C. Para-aminobenzoic acid
D. Tetrahydrofolate
E. Thymidylic acid

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- A. Dihydrofolate polyglutamate (50%)
- B. Folinic acid (6%)
- C. ~~Para-aminobenzoic acid~~ (8%)
- D. ~~Tetrahydrofolate~~ (29%)
- E. ~~Thymidylic acid~~ (5%)

Correct

50%
Answered correctly

48 secs
Time Spent

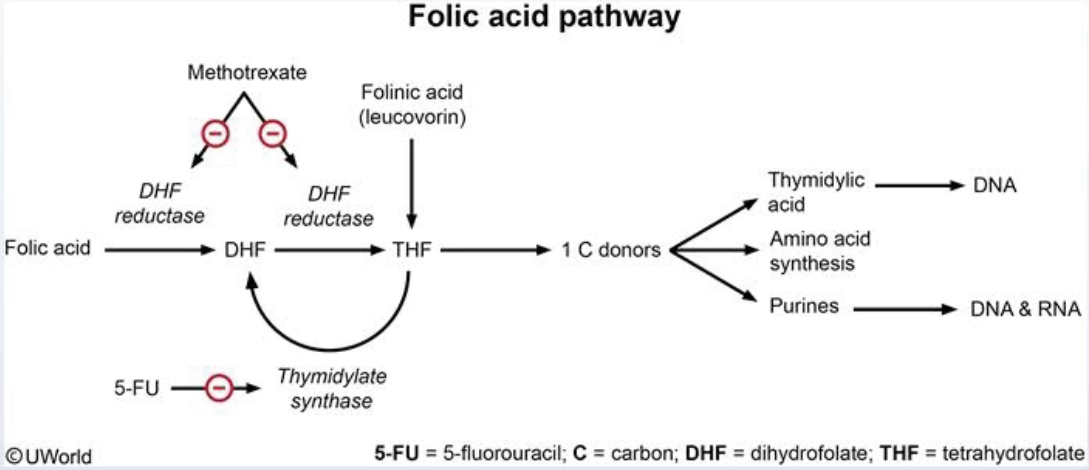
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Answered correctly
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Explanation



Methotrexate (MTX), a **folate antagonist**, is the drug of choice for non-surgical treatment of an early, unruptured ectopic pregnancy. Folic acid is a required precursor to nucleic acid synthesis. Barriers to its metabolism are especially effective in hindering the growth of rapidly proliferating cells such as in a

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5-FU = 5-fluorouracil; **C** = carbon; **DHF** = dihydrofolate; **THF** = tetrahydrofolate

Methotrexate (MTX), a **folate antagonist**, is the drug of choice for non-surgical treatment of an early, unruptured ectopic pregnancy. Folic acid is a required precursor to nucleic acid synthesis. Barriers to its metabolism are especially effective in hindering the growth of rapidly proliferating cells such as in a developing embryo or certain types of cancer.

Normally, folic acid is reduced to dihydrofolate (DHF) by dihydrofolate reductase and then reduced further to **tetrahydrofolate** (THF), an integral precursor of **DNA synthesis**. MTX is structurally similar to folic acid and competitively and irreversibly **inhibits DHF reductase**. DHF reductase inhibition prevents the formation of THF **(Choice D)**.

After entering the target cell, MTX undergoes **polyglutamation**, which prevents the movement of MTX out of the cell, resulting in intracellular accumulation of MTX for later use. Similarly, folate and recycled DHF are stored within the cell via polyglutamation. Because MTX inhibits DHF reductase, folic acid and DHF polyglutamate will accumulate in cells.

(Choice B) Folinic acid (leucovorin) is a reduced form of folic acid that can be used to counter the toxic effects of MTX chemotherapy. Folinic acid selectively "rescues" normal cells by competing with MTX for DHF reductase binding sites. It can reactivate DHF reductase, therefore allowing re-initiation of DNA

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(Choice B) Folinic acid (leucovorin) is a reduced form of folic acid that can be used to counter the toxic effects of MTX chemotherapy. Folinic acid selectively "rescues" normal cells by competing with MTX for DHF reductase binding sites. It can reactivate DHF reductase, therefore allowing re-initiation of DNA synthesis.

(Choice C) Para-aminobenzoic acid (PABA) is a folic acid precursor in prokaryotes. Sulfonamide antibiotics are chemical analogues of PABA that inhibit the enzyme dihydropteroate synthetase, preventing bacterial conversion of PABA to folic acid. Humans lack the ability to convert PABA to folic acid and require dietary folate.

(Choice E) Thymidylic acid is a nucleotide that contributes to pyrimidine formation. Its synthesis is inhibited by MTX.

Educational objective:

Methotrexate is a folic acid antagonist used to treat ectopic pregnancy. It competitively inhibits the enzyme dihydrofolate (DHF) reductase, which catalyzes the synthesis of tetrahydrofolate. DHF reductase inhibition causes the intermediate DHF to accumulate intracellularly.

References

- Methotrexate: the pharmacology behind medical treatment for ectopic pregnancy.

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A 42-year-old previously healthy woman comes to the office due to fever and sore throat. She has no cough. Physical examination shows tonsillar exudate and a nontender cervical lymph node that measures 3.5 cm in diameter. Oral antibiotic therapy is started and on a follow-up visit a week later, the patient reports that her symptoms have resolved. The previously enlarged cervical lymph node has decreased slightly in size. On several follow-up visits over the following year, the patient remains asymptomatic and the size of the lymph node fluctuates but does not disappear completely. Referral to a surgeon is made and excisional biopsy of the lymph node is performed. Which of the following is the most likely diagnosis?

A. Acute lymphoblastic leukemia
B. Burkitt lymphoma
C. Diffuse large B-cell lymphoma
D. Follicular lymphoma
E. Hairy cell leukemia
F. Mycosis fungoides

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A. ~~Acute lymphoblastic leukemia~~ (1%)
B. ~~Burkitt lymphoma~~ (16%)
C. Diffuse large B-cell lymphoma (13%)
D. Follicular lymphoma (59%)
E. Hairy cell leukemia (2%)
F. ~~Mycosis fungoides~~ (6%)

Incorrect
Correct answer

59%

02 mins, 44 secs

01/05/2021

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This patient with persistent fluctuating lymphadenopathy, who may have had an unrelated pharyngitis (treated with antibiotics) on initial presentation, most likely has **follicular lymphoma**. Follicular lymphoma is the most common **indolent** non-Hodgkin lymphoma (NHL) in adults and the second most common NHL overall (after diffuse Large B cell lymphoma). It derives from germinal center B cells and typically has a long, **waxing and waning** clinical course.

The condition most often presents in middle-aged patients with **painless lymph node enlargement** or abdominal discomfort from an abdominal mass. Histology is notable for a nodular pattern, and the neoplastic follicles are composed of a mixture of centrocytes (cleaved cells) and centroblasts (noncleaved cells). The majority of tumors exhibit a **t(14;18) translocation**, resulting in overexpression of the *BCL2* oncogene that blocks programmed cell death.

(Choice A) Acute lymphoblastic leukemia/lymphoma is the most common malignancy in children. It presents with lymphadenopathy, hepatosplenomegaly, fever, bleeding, and bone pain. Neoplastic cells are pre-B or pre-T cells (lymphoblasts).

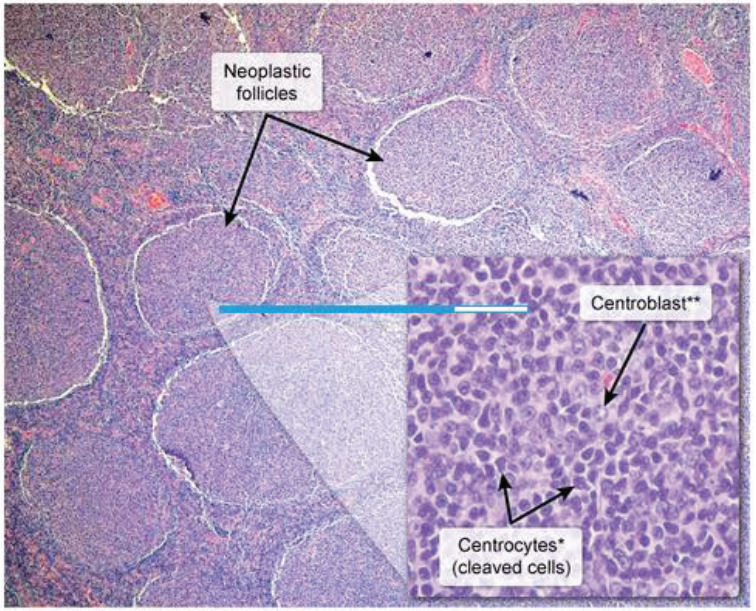
(Choice B) Burkitt lymphoma is a highly aggressive (but generally chemotherapy-responsive) B-cell NHL associated with chronic Epstein-Barr virus infection and/or deregulation of the *MYC* proto-oncogene. Patients typically develop rapidly growing tumor masses in the facial bones, jaw, or abdomen. Tumor

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Exhibit Display

Follicular lymphoma



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Patients typically develop rapidly growing tumor masses in the facial bones, jaw, or abdomen. Tumor

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(Choice B) Burkitt lymphoma is a highly aggressive (but generally chemotherapy-responsive) B-cell NHL associated with chronic Epstein-Barr virus infection and/or deregulation of the *MYC* proto-oncogene. Patients typically develop rapidly growing tumor masses in the facial bones, jaw, or abdomen. Tumor doubling time is very rapid and spontaneous tumor lysis can occur.

(Choice C) Diffuse large B-cell lymphoma typically presents with a rapidly enlarging nodal (neck, abdomen, mediastinum) or extranodal symptomatic mass. The Waldeyer's ring (oropharyngeal lymphoid tissue) and gastrointestinal tract are commonly involved, and systemic "B" symptoms (fever, weight loss, drenching night sweats) can also be seen.

(Choice E) Hairy cell leukemia, a mature B-cell neoplasm, presents with splenomegaly and pancytopenia most often in older men. Lymph node enlargement is not characteristic. Leukemic cells have hairlike cytoplasmic projections and are positive for tartrate-resistant acid phosphatase (TRAP).

(Choice F) Mycosis fungoides is a cutaneous T-cell lymphoma. Proliferating $CD4^+$ atypical lymphocytes infiltrate the dermis and epidermis, where they form Pautrier microabscesses. This condition manifests with plaques (often on trunk or buttocks) that may be confused with eczema or psoriasis. Generalized erythema and scaling and thickening of the skin (erythroderma) may result.

Educational objective:

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Educational objective:

Follicular lymphoma is the most common indolent non-Hodgkin lymphoma in adults. It is of B-cell origin and presents with painless waxing and waning (ie, fluctuating) lymphadenopathy. The cytogenetic change t(14;18) is characteristic and results in overexpression of the *BCL2* oncogene.

References

- Follicular lymphoma: 2014 update on diagnosis and management.

Pathology	Hematology & Oncology	Nonhodgkin lymphoma
Subject	System	Topic

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A 25-year-old woman is brought to the emergency department after a motor vehicle collision. She has a pneumothorax, multiple rib fractures, and a right femur and tibial fracture. A chest tube is placed. The patient receives resuscitation and undergoes repair of the femur and tibial fractures. The following day, she develops respiratory distress, decreased urine output, and persistent bleeding from the chest tube drains and around the intravenous lines. Which of the following sets of laboratory findings is most likely to be seen in this patient?

	Fibrinogen	Protein C	Factor VII
A.	↓	↓	↓
B.	↓	↓	↑
C.	↓	↑	↑
D.	↓	↑	↓
E.	↑	↑	↑

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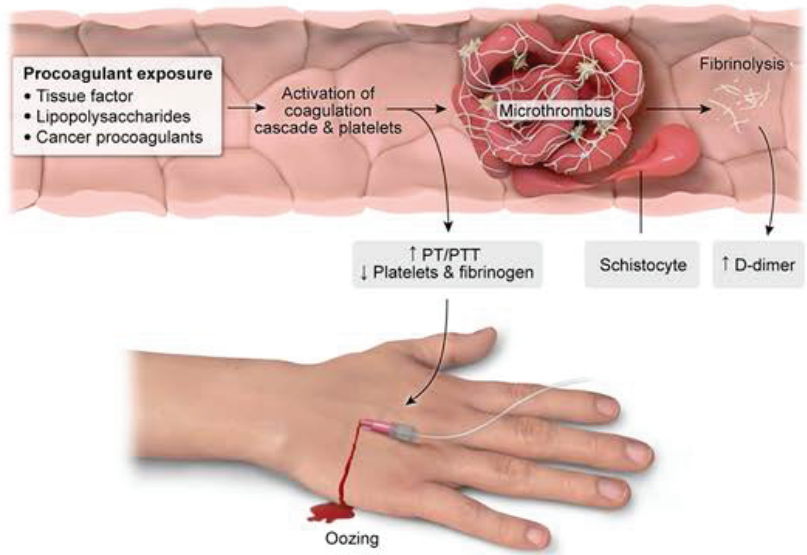
	Fibrinogen	Protein C	Factor VII	
✓ A.	↓	↓	↓	(60%)
B.	↓	↓	↑	(6%)
C.	↓	↑	↑	(4%)
D.	↓	↑	↓	(24%)
E.	↑	↑	↑	(3%)

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Exhibit Display

Acute disseminated intravascular coagulation



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This patient with multiple injuries following a severe motor vehicle accident developed respiratory distress, reduced renal output, and oozing from the catheter and venipuncture sites. This presentation raises strong suspicion for **disseminated intravascular coagulation** (DIC), a consumptive coagulopathy associated with **trauma**, sepsis, malignancy, and obstetrical complications.

In DIC due to trauma, the coagulation cascade is triggered by damage to the vascular endothelium (exposes tissue factor) and tissues (releases procoagulant proteins and phospholipids). This leads to the generation of fibrin- and platelet-rich **microvascular thrombi**, which consumes platelets, coagulation factors (eg, **low factor VII**), and fibrinogen. Fibrinolysis and anticoagulant proteins then dissolve the clots, which **depletes protein C**, protein S, and antithrombin.

Most patients with acute DIC develop **bleeding complications** such as **oozing from catheters/venipuncture sites**, ecchymosis, and petechiae. End organ damage to the kidneys (eg, renal insufficiency) and lungs (eg, pulmonary hemorrhage) is common. Many patients also have microangiopathic hemolytic anemia (eg, schistocytes) due to shearing of red blood cells by intravascular thrombi.

Educational objective:
Acute disseminated intravascular coagulation is a consumptive coagulopathy linked to severe trauma.

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Educational objective:
Acute disseminated intravascular coagulation is a consumptive coagulopathy linked to severe trauma. Widespread formation of microvascular thrombi leads to consumption of platelets, coagulation factors, and fibrinogen. Subsequent activation of anticoagulant proteins leads to low protein C/S; fibrinolysis elevates D-dimer. Most patients have bleeding complications (eg, oozing from venipuncture/catheter sites) and end organ damage to the lungs or kidneys.

Pathology | Hematology & Oncology | DIC

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A 66-year-old woman comes to the office due to 2 months of worsening fatigue and dyspnea with moderate exertion. The patient has a history of breast cancer treated with surgery and combination chemotherapy 6 years ago. She has no other medical conditions. Vital signs are within normal limits. Physical examination reveals normal jugular venous pressure, clear lungs, and normal heart sounds; there is no hepatosplenomegaly, lymphadenopathy, or extremity edema. Laboratory results are as follows:

Hemoglobin	7.2 g/dL
Mean corpuscular volume	108 μm^3
Reticulocytes	1%
Platelets	90,000/mm^3
Leukocytes	3,800/mm^3

Peripheral blood smear shows oval macrocytic red cells and hyposegmented neutrophils. Bone marrow biopsy of this patient is most likely to reveal which of the following?

A. Deposits of atypical gland-forming cells

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Mean corpuscular volume	108 μm³
Reticulocytes	1%
Platelets	90,000/mm³
Leukocytes	3,800/mm³

Peripheral blood smear shows oval macrocytic red cells and hyposegmented neutrophils. Bone marrow biopsy of this patient is most likely to reveal which of the following?

A. Deposits of atypical gland-forming cells
B. Dysplastic erythroid and myeloid progenitor cells
C. Hypercellular marrow containing sheets of plasma cells
D. Increased macrophage iron with absent sideroblasts
E. Large collagen bands replacing the entire marrow

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Mean corpuscular volume	108 μm³
Reticulocytes	1%
Platelets	90,000/mm³
Leukocytes	3,800/mm³

Peripheral blood smear shows oval macrocytic red cells and hyposegmented neutrophils. Bone marrow biopsy of this patient is most likely to reveal which of the following?

A. Deposits of atypical gland-forming cells (4%)
B. Dysplastic erythroid and myeloid progenitor cells (42%)
C. Hypercellular marrow containing sheets of plasma cells (6%)
D. ~~Increased macrophage iron with absent sideroblasts~~ (5%)
E. Large collagen bands replacing the entire marrow (40%)

Incorrect
Correct answer

42%
Answered correctly

01 min, 58 secs
Time Spent

12/13/2020
Last Updated

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Myelodysplastic syndrome	
Epidemiology	• Clonal hematopoietic malignancy • Seen primarily with advanced age or previous chemotherapy or radiation treatment • Can transform to acute myelogenous leukemia
Manifestations	• ≥1 types of cytopenia: ◦ Anemia: weakness, fatigue ◦ Leukopenia: infections ◦ Thrombocytopenia: bruising, bleeding • Hepatosplenomegaly & lymphadenopathy are uncommon
	• Peripheral blood smear: dysplastic erythrocytes

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Epidemiology	previous chemotherapy or radiation treatment • Can transform to acute myelogenous leukemia
Manifestations	• ≥1 types of cytopenia: ◦ Anemia: weakness, fatigue ◦ Leukopenia: infections ◦ Thrombocytopenia: bruising, bleeding • Hepatosplenomegaly & lymphadenopathy are uncommon
Evaluation	• Peripheral blood smear: dysplastic erythrocytes (eg, oval macrocytosis) & neutrophils (eg, hyposegmentation, hypogranulation) • Bone marrow biopsy: single or multilineage dysplasia with hypercellularity

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This patient's previous chemotherapy, pancytopenia, and cellular dysplasia (eg, hyposegmented neutrophils, oval macrocytic erythrocytes) indicate likely **myelodysplastic syndrome** (MDS). MDS is a **clonal hematologic malignancy** associated with the development of driver mutations due to **advanced age**, previous **chemo-/radiotherapy**, or exposure to environmental toxins.

MDS is marked by the following:

- **≥1 cytopenias:** normal hematopoiesis is impaired due to neoplastic cell replication in the bone marrow; therefore, patients usually present with symptoms of ≥1 cytopenia such as fatigue/dyspnea on exertion (anemia), bleeding/bruising (thrombocytopenia), or infections (leukopenia). Because erythrocyte production is impaired, **reticulocyte count will be low** despite significant anemia. However, significant extramedullary hematopoiesis does not occur, so **hepatosplenomegaly is rare**.
- **Dysplasia of erythrocytes and neutrophils**: peripheral blood smear usually shows normocytic or macrocytic erythrocytes with a variety of abnormalities (eg, **oval macrocytes**). Neutrophils are typically hypolobulated and hypogranular.

Bone marrow biopsy typically reveals a **hypercellular** marrow with **dysplasia** of ≥1 cell lines. **Myeloblasts are increased** (but <20% of total cells), and granulocytes show evidence of **impaired maturation** such as

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Bone marrow biopsy typically reveals a **hypercellular** marrow with **dysplasia** of ≥1 cell lines. **Myeloblasts are increased** (but <20% of total cells), and granulocytes show evidence of **impaired maturation** such as abnormalities in size, granulation, or lobulation. Erythrocytes also show signs of abnormal development, including large size and nuclear lobation/budding.

(Choice A) Metastatic adenocarcinoma (atypical gland-forming cells) can infiltrate the bone marrow, leading to pancytopenia. Although reticulocytes would be diminished, peripheral blood smear would not show signs of abnormal granulocyte development (eg, hyposegmentation).

(Choice C) Hypercellular marrow with sheets of plasma cells is seen in multiple myeloma. Although it occasionally causes pancytopenia (anemia alone is more common), peripheral smear shows rouleaux formation due to increased monoclonal proteins; dysmorphic granulocytes would not be seen. In addition, multiple myeloma is not strongly associated with chemotherapy exposure.

(Choice D) Anemia of chronic disease is associated with increased retention of iron in reticuloendothelial macrophages. Although low reticulocyte count is common, patients usually have normocytic anemia and relatively normal peripheral smear findings (eg, no dysplasia). In contrast, MDS can be associated with ringed sideroblasts (iron-laden erythrocyte precursors) in the bone marrow.

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(Choice D) Anemia of chronic disease is associated with increased retention of iron in reticuloendothelial macrophages. Although low reticulocyte count is common, patients usually have normocytic anemia and relatively normal peripheral smear findings (eg, no dysplasia). In contrast, MDS can be associated with ringed sideroblasts (iron-laden erythrocyte precursors) in the bone marrow.

(Choice E) Collagen deposition in the bone marrow is associated with myelofibrosis, a chronic myeloproliferative disorder that causes anemia and variable platelet/leukocyte counts. However, patients typically have marked splenomegaly due to extramedullary hematopoiesis.

Educational objective:
Myelodysplastic syndrome is a clonal hematologic neoplasm marked by ≥1 cytopenias and cellular dysplasia (eg, oval macrocytic erythrocytes, hyposegmented granulocytes). Bone marrow evaluation usually reveals a hypercellular marrow, a mild or moderate increase in myeloblasts (<20% of total cells), and dysplastic erythrocytes/granulocytes.

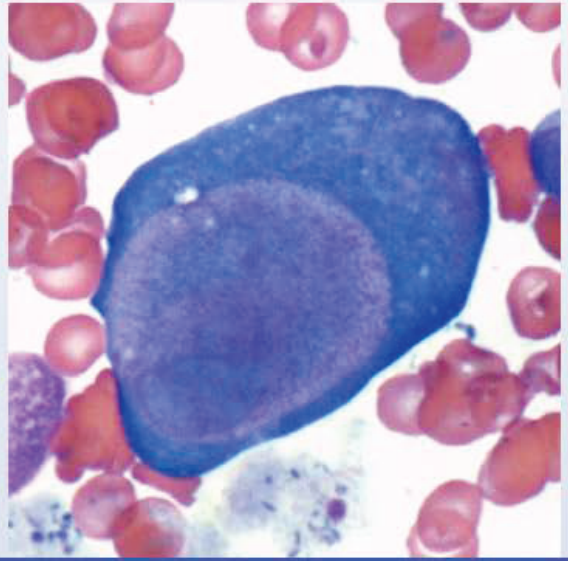
Pathology	Hematology & Oncology	Myelodysplastic syndrome
Subject	System	Topic

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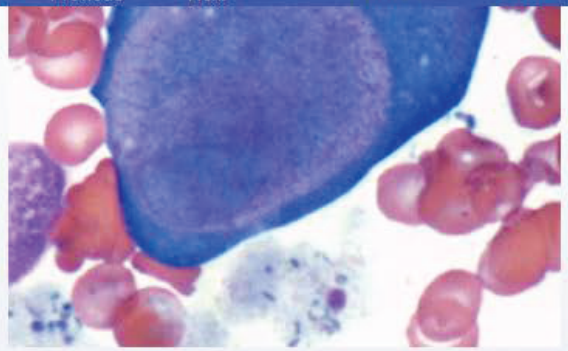
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A 12-year-old girl is brought to the emergency department due to several days of worsening exertional dyspnea and lethargy. The patient has a history of sickle cell disease and takes hydroxyurea. Physical examination shows mucosal pallor and a systolic ejection murmur. Laboratory studies reveal a hemoglobin level of 5.6 g/dL. Bone marrow biopsy is performed and demonstrates decreased erythroid precursors and giant pronormoblasts containing inclusions, as shown below.



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Which of the following is the most likely cause of this patient's current condition?

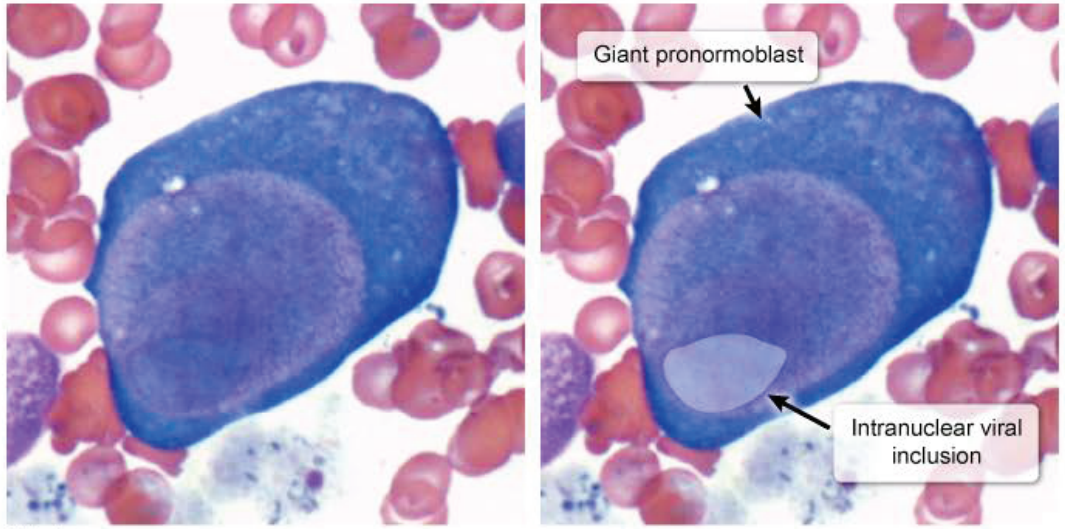
- A. Acute viral infection (54%)
- B. Dietary folate deficiency (6%)
- C. Medication adverse effect (33%)
- D. Secondary iron overload (4%)
- E. Toxic chemical exposure (2%)

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Explanation

Parvovirus B19 infection



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This patient's symptomatic anemia (lethargy, exertional dyspnea, mucosal pallor, ejection murmur) and bone marrow biopsy showing decreased erythropoiesis (reduced erythrocyte precursors) raise suspicion for **transient aplastic crisis** due to acute **parvovirus B19 infection**.

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This patient's symptomatic anemia (lethargy, exertional dyspnea, mucosal pallor, ejection murmur) and bone marrow biopsy showing decreased erythropoiesis (reduced erythrocyte precursors) raise suspicion for **transient aplastic crisis** due to acute **parvovirus B19 infection**.

Parvovirus is a small, nonenveloped, DNA virus transmitted via the respiratory route that primarily attacks erythroid progenitor cells due to tropism for an erythrocyte cell surface receptor (P blood group antigen). Infection of erythroid progenitor cells **prevents red blood cell maturation**, leading to formation of abnormal **giant pronormoblasts** (several times larger than surrounding red blood cells) with glassy, intranuclear viral inclusions. The drop in red cell production often leads to a transient (1-2 week) drop in hematocrit. Although many patients are asymptomatic, individuals with underlying hemoglobin disorders (eg, **sickle cell anemia**) sometimes develop **symptomatic anemia**.

(Choice B) Folate deficiency can be seen in patients with sickle cell disease due to increased erythropoiesis in response to chronic anemia. However, folate deficiency is characterized by macrocytic anemia and hypersegmented neutrophils; giant pronormoblasts with inclusions would not be seen.

(Choice C) Hydroxyurea can sometimes interfere with normal erythropoiesis and result in macrocytic anemia. However, it is not associated with giant pronormoblasts with intranuclear inclusions.

(Choice D) Patients with sickle cell disease who require repeated blood transfusion can sometimes

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erythropoiesis in response to chronic anemia. However, folate deficiency is characterized by macrocytic anemia and hypersegmented neutrophils; giant pronormoblasts with inclusions would not be seen.

(Choice C) Hydroxyurea can sometimes interfere with normal erythropoiesis and result in macrocytic anemia. However, it is not associated with giant pronormoblasts with intranuclear inclusions.

(Choice D) Patients with sickle cell disease who require repeated blood transfusion can sometimes develop secondary iron overload. Bone marrow biopsy would show increased iron stores.

(Choice E) Exposure to toxic chemicals (eg, industrial solvents/chemicals, insecticides) can lead to aplastic anemia. However, bone marrow biopsy would show hypocellular marrow with a decrease in all cell types; the remaining hematopoietic cells would be morphologically normal.

Educational objective:
Parvovirus B19 infection can cause transient aplastic crisis, particularly in those with underlying hemoglobin disorders such as sickle cell anemia. Patients develop symptomatic anemia (eg, exertional dyspnea, fatigue, low hematocrit) due to inhibition of erythropoiesis by the virus. Bone marrow examination will show giant pronormoblasts with glassy, intranuclear viral inclusions.

Pathology	Hematology & Oncology	Sickle cell
Subject	System	Topic

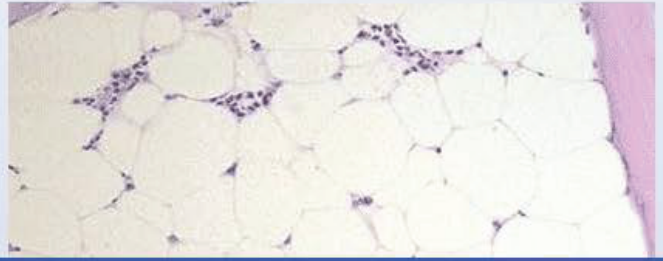
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A 7-year-old boy is brought to the office due to fatigue, easy bruising, and frequent epistaxis for 2 weeks. He has no medical problems and takes no medications. His temperature is 36.7 C (98 F), blood pressure is 90/60 mm Hg, pulse is 94/min, and respirations are 18/min. Physical examination reveals pallor and multiple ecchymoses. There is no lymphadenopathy or hepatosplenomegaly. Laboratory results are as follows:

Hemoglobin	8.2 g/L
Platelets	40,000/mm^3
Leukocytes	2,100/mm^3

A bone marrow biopsy is shown in the image below. Which of the following is the most likely diagnosis?

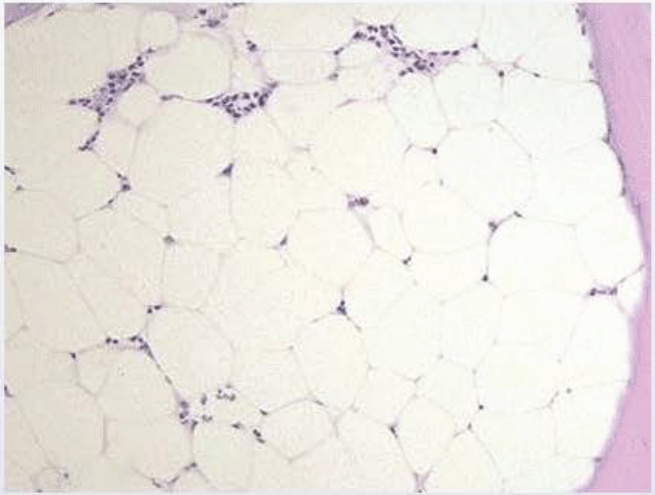


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Leukocytes 2,100/mm^3

A bone marrow biopsy is shown in the image below. Which of the following is the most likely diagnosis?

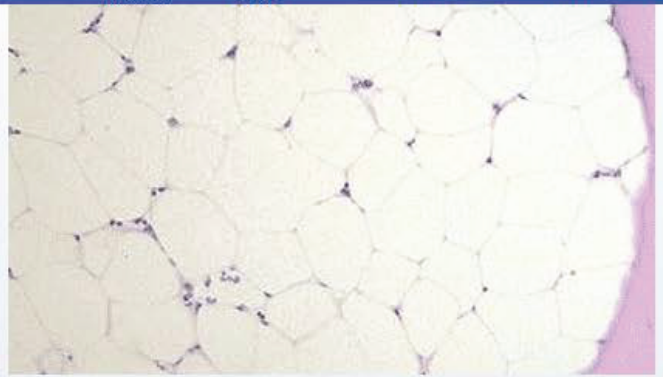


A. Acute lymphoblastic leukemia

B. Fanconi anemia

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A. Acute lymphoblastic leukemia

B. Fanconi anemia

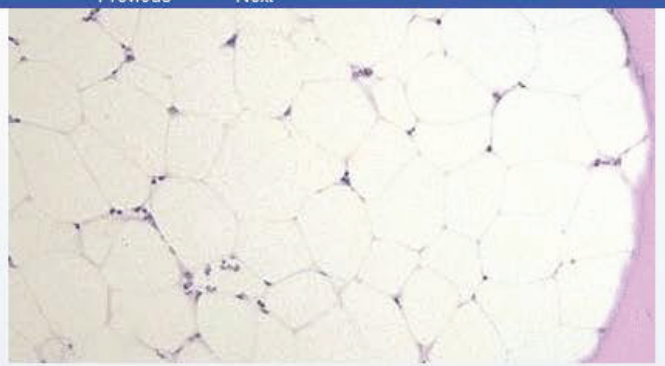
C. Idiopathic aplastic anemia

D. Myelodysplastic syndrome

E. Parvovirus B19 infection

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A. Acute lymphoblastic leukemia (3%)

B. Fanconi anemia (6%)

C. Idiopathic aplastic anemia (61%)

D. Myelodysplastic syndrome (11%)

E. Parvovirus B19 infection (15%)

Correct

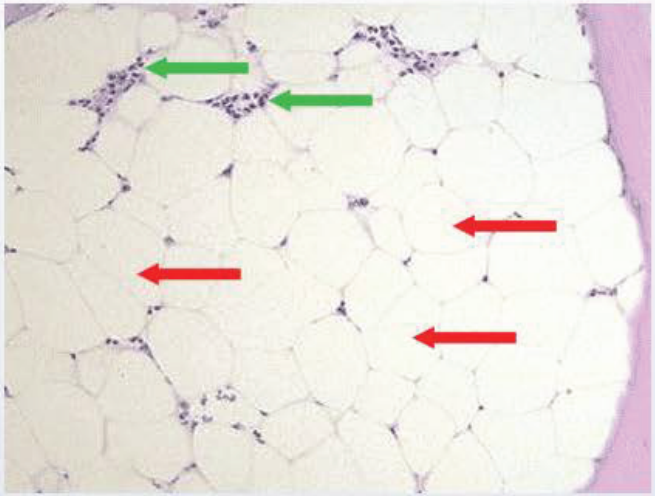
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Explanation



Aplastic anemia (AA) is defined by **pancytopenia** with **bone marrow hypocellularity**. Bone marrow biopsy, shown in the image above, reveals an abundance of fat cells (red arrows) and scattered clusters of morphologically normal white blood cells (green arrows). This hypocellularity contrasts with healthy bone marrow, which has an approximate 1:1 ratio of fat to hematopoietic elements.

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Aplastic anemia (AA) is defined by **pancytopenia** with **bone marrow hypocellularity**. Bone marrow biopsy, shown in the image above, reveals an abundance of fat cells (red arrows) and scattered clusters of morphologically normal white blood cells (green arrows). This hypocellularity contrasts with healthy bone marrow, which has an approximate 1:1 ratio of fat to hematopoietic elements.

Most cases of AA are **acquired** from a direct toxic insult or T-cell response leading to apoptosis of pluripotent stem cells. The etiology is unknown in most children, but the damage may result from drug exposures (eg, chemotherapy, benzene [gasoline, tobacco smoke], carbamazepine [anti-epileptic]) and viral infections (eg, hepatitis, Epstein-Barr virus).

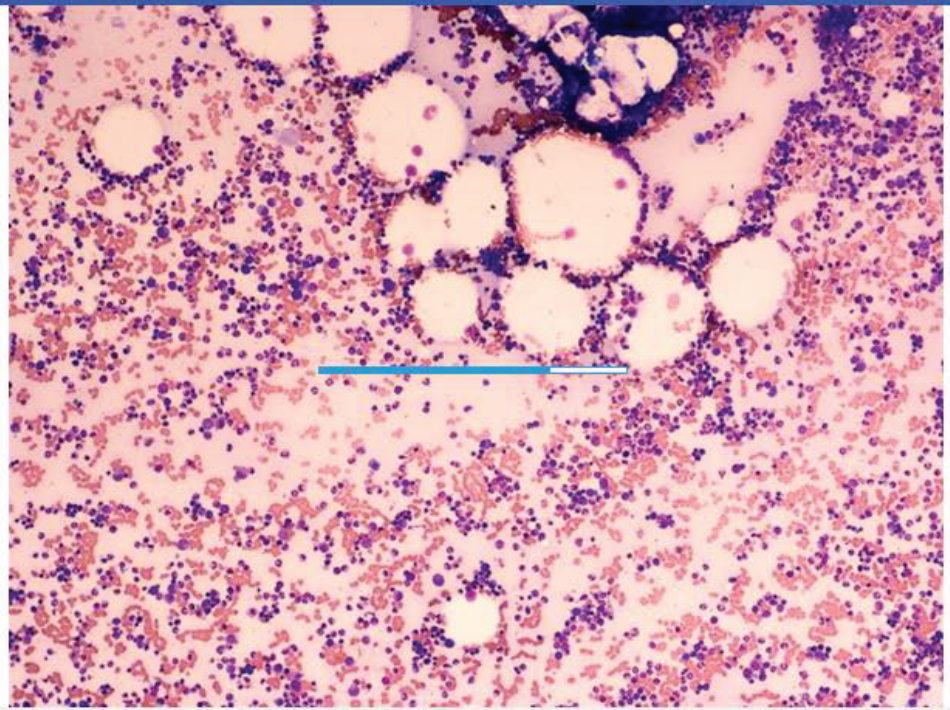
AA presents with progressive signs and symptoms of pancytopenia, such as bleeding from thrombocytopenia, pallor and fatigue from anemia, and bacterial infections from leukopenia/neutropenia. Splenomegaly is notably absent due to a lack of available hematopoietic progenitor cells and, therefore, a lack of extramedullary hematopoiesis.

(Choice A) Acute lymphoblastic leukemia is the most common childhood malignancy. It can present with lymphadenopathy and hepatosplenomegaly due to leukemic cell infiltration as well as anemia,

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lymphadenopathy and hepatosplenomegaly due to leukemic cell infiltration as well as anemia,

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lack of extramedullary hematopoiesis.

(Choice A) Acute lymphoblastic leukemia is the most common childhood malignancy. It can present with lymphadenopathy and hepatosplenomegaly due to leukemic cell infiltration as well as anemia, thrombocytopenia, and leukopenia/leukocytosis. Hypercellularity and lymphoblasts (immature lymphocytes [black arrows]) are noted on bone marrow aspirate.

(Choice B) Fanconi anemia is an inherited cause of AA that presents with short stature and absent thumbs and is associated with an increased risk of malignancy (eg, myelodysplastic syndrome, acute myeloid leukemia).

(Choice D) Myelodysplastic syndrome (MDS) is caused by a defect in stem cell maturation leading to ineffective differentiation of cell lines and, therefore, pancytopenia. Bone marrow biopsy will be hypercellular with abnormally differentiated cells (eg, misshapen nuclei). MDS primarily occurs in patients age ≥65.

(Choice E) Parvovirus B19 infects erythrocyte precursors and can cause an aplastic crisis (red cell aplasia only) in patients with preexisting hematologic disease (eg, sickle cell anemia, hereditary spherocytosis). Leukopenia and thrombocytopenia can also be found in immunocompromised patients.

Educational objective:

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thumbs and is associated with an increased risk of malignancy (eg, myelodysplastic syndrome, acute myeloid leukemia).

(Choice D) Myelodysplastic syndrome (MDS) is caused by a defect in stem cell maturation leading to ineffective differentiation of cell lines and, therefore, pancytopenia. Bone marrow biopsy will be hypercellular with abnormally differentiated cells (eg, misshapen nuclei). MDS primarily occurs in patients age ≥65.

(Choice E) Parvovirus B19 infects erythrocyte precursors and can cause an aplastic crisis (red cell aplasia only) in patients with preexisting hematologic disease (eg, sickle cell anemia, hereditary spherocytosis). Leukopenia and thrombocytopenia can also be found in immunocompromised patients.

Educational objective:

Aplastic anemia is most commonly due to a toxic effect or autoimmune response causing apoptosis of pluripotent stem cells (pancytopenia). Bone marrow biopsy reveals hypocellularity with an abundance of fat cells.

References

- Idiopathic aplastic anemia: diagnosis and classification.

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A 36-year-old woman comes to the office due to 2 weeks of fatigue and easy bruising. She also had an upper respiratory tract infection recently. Physical examination shows no lymphadenopathy and no hepatosplenomegaly. Laboratory studies are as follows:

Hemoglobin	7.0 g/dL
Erythrocytes	1.8 million/mm^3
Mean corpuscular volume	90 µm^3
Reticulocytes	0.1%
Platelets	88,000/mm^3
Leukocytes	2,500/mm^3
Prothrombin time	13 seconds
Partial thromboplastin time	30 seconds

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Leukocytes	2,500/mm^3
Prothrombin time	13 seconds
Partial thromboplastin time	30 seconds

A peripheral blood smear shows normocytic, normochromic red blood cells. The other cell types are also morphologically normal. Bone marrow biopsy in this patient would most likely show which of the following patterns?

A. Hypercellular marrow filled with numerous blast forms
B. Hypercellular marrow with megaloblastic hematopoiesis
C. Hypergranular promyelocytes with multiple Auer rods
D. Hypocellular marrow filled with fat cells and marrow stroma

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Leukocytes	2,500/mm^3
Prothrombin time	13 seconds
Partial thromboplastin time	30 seconds

A peripheral blood smear shows normocytic, normochromic red blood cells. The other cell types are also morphologically normal. Bone marrow biopsy in this patient would most likely show which of the following patterns?

A. Hypercellular marrow filled with numerous blast forms (9%)

B. Hypercellular marrow with megaloblastic hematopoiesis (5%)

C. Hypergranular promyelocytes with multiple Auer rods (6%)

D. Hypocellular marrow filled with fat cells and marrow stroma (79%)

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Aplastic anemia	
Pathogenesis	Bone marrow failure due to hematopoietic stem cell deficiency ($CD34^+$)
Causes	• Autoimmune • Infections (eg, HIV, Epstein-Barr virus) • Drugs (eg, carbamazepine, chloramphenicol, sulfonamides) • Exposure to radiation or toxins (eg, benzene, solvents)
Clinical & laboratory findings	Laboratory studies: pancytopenia • Anemia (fatigue, weakness, pallor) • Thrombocytopenia (mucosal bleeding, easy bruising, petechiae) • Leukopenia (recurrent infections) Biopsy: hypocellular bone marrow with fat & stromal cells

This patient has anemia (manifesting as fatigue), thrombocytopenia (easy bruising), and neutropenia (recent respiratory infection), with profound reticulocytopenia, morphologically normal cell lines on peripheral smear, and no splenomegaly on physical examination. This presentation is most consistent with

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This patient has anemia (manifesting as fatigue), thrombocytopenia (easy bruising), and neutropenia (recent respiratory infection), with profound reticulocytopenia, morphologically normal cell lines on peripheral smear, and no splenomegaly on physical examination. This presentation is most consistent with **aplastic anemia**, which in actuality presents as **pancytopenia** (not simply anemia) that is characteristically **without splenomegaly**. Bone marrow examination reveals **marked hypocellularity** with the hematopoietic elements replaced by fat cells and marrow stroma; aspiration typically produces a "dry tap." The absence of splenomegaly is key in diagnosing aplastic anemia; a patient with pancytopenia and splenomegaly is very unlikely to have aplastic anemia.

Other causes of pancytopenia without splenomegaly include severe vitamin B_{12} and folic acid deficiency anemia, acute leukemias, and certain forms of myelodysplastic syndrome (MDS). Bone marrow examination can be extremely helpful in distinguishing among these conditions.

(Choice A) Hypercellular marrow with increased blasts can be found in myeloproliferative disorders such as primary myelofibrosis (would present with splenomegaly and fatigue) or chronic myelogenous leukemia (would present with leukocytosis), MDS (would present in older patients), and certain leukemias (eg, acute myeloid leukemia [AML] - blasts would be seen on peripheral smear).

(Choice B) Hypercellular marrow with megaloblastic hematopoiesis can be seen in MDS or megaloblastic anemia. However, MDS typically occurs in elderly patients (median age ~65) and has a male

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myeloid leukemia [AML] - blasts would be seen on peripheral smear).

(Choice B) Hypercellular marrow with megaloblastic hematopoiesis can be seen in MDS or megaloblastic anemia. However, MDS typically occurs in elderly patients (median age ~65) and has a male predominance. Patients with severe megaloblastic anemia usually have macrocytosis rather than normocytosis.

(Choice C) Acute promyelocytic (FAB M3) leukemia is characterized by the presence of promyelocytes with Auer rods (rod-shaped cytoplasmic inclusions). The cell cytoplasm also has numerous coarse azurophilic granules. This type of AML is characterized clinically by disseminated intravascular coagulation (acquired hypercoagulability and bleeding), which is not seen in this patient (given her normal prothrombin time and partial thromboplastin time); immature white blood cell forms would also be present on peripheral smear.

Educational objective:
Aplastic anemia causes pancytopenia as the bone marrow is replaced by fat cells and marrow stroma. The absence of splenomegaly on physical examination is characteristic. A bone marrow biopsy can be extremely useful in making the diagnosis.

Pathology Hematology & Oncology Aplastic anemia

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A 3-year-old boy is brought to clinic by his mother due to fevers. Three weeks ago, the patient developed a fever, cough, and runny nose. He attends day care, where several children have had viral upper respiratory infections. Symptoms had briefly resolved 10 days ago, but the fever recurred last week after the patient returned to day care. Since then, he has been home due to fever occurring almost daily despite acetaminophen administration. Temperature is 38.3 C (100.9 F). Examination shows enlarged lymph nodes in the neck region. Lymphadenopathy at which of the following locations is most concerning for malignancy rather than infection in this patient?

A. Anterior cervical
B. Posterior cervical
C. Submandibular
D. Submental
E. Supraclavicular

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A 3-year-old boy is brought to clinic by his mother due to fevers. Three weeks ago, the patient developed a fever, cough, and runny nose. He attends day care, where several children have had viral upper respiratory infections. Symptoms had briefly resolved 10 days ago, but the fever recurred last week after the patient returned to day care. Since then, he has been home due to fever occurring almost daily despite acetaminophen administration. Temperature is 38.3 C (100.9 F). Examination shows enlarged lymph nodes in the neck region. Lymphadenopathy at which of the following locations is most concerning for malignancy rather than infection in this patient?

A. Anterior cervical (10%)
B. Posterior cervical (13%)
C. Submandibular (12%)
D. Submental (2%)
E. Supraclavicular (61%)

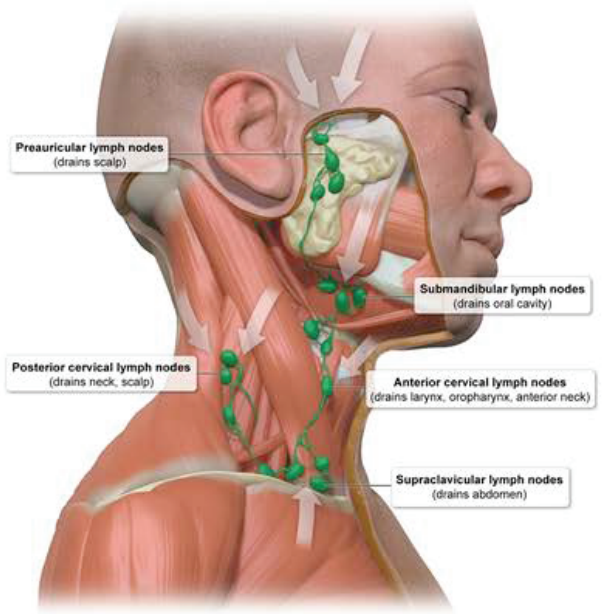
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Head & neck lymph node drainage



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Lymph node enlargement (lymphadenopathy) of the head and neck is common in children due to frequent exposure to infections (eg, pharyngitis, upper respiratory infections). The lymphatic system drains bacteria and cellular debris through local lymph nodes, which filter foreign material and contain lymphocytes to fight infection. Lymph then drains to the thoracic and right lymphatic ducts, which empty into the subclavian veins.

Although lymphadenopathy usually occurs secondary to the proliferation of inflammatory cells in response to infection, it is less commonly due to a clonal expansion of malignant cells. **Malignancy** should be suspected when lymph node enlargement is associated with any of the following features:

- Generalized or supraclavicular location
- Firm, **immobile**, nontender quality
- >2 cm or **increasing size**
- Systemic features (eg, weight loss, night sweats)

The **supraclavicular nodes** drain the **chest** (ie, pulmonary system, mediastinum) and **abdomen** (ie, gastrointestinal and genitourinary tracts). Therefore, enlargement of these lymph nodes is **unlikely** to be

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The **supraclavicular nodes** drain the **chest** (ie, pulmonary system, mediastinum) and **abdomen** (ie, gastrointestinal and genitourinary tracts). Therefore, enlargement of these lymph nodes is **unlikely** to be caused by common **childhood infections** and always warrants further workup (eg, complete blood count, ultrasound) for an associated malignancy.

(Choices A and B) Anterior and posterior cervical lymphadenopathy is common with upper respiratory infections because these nodes drain the neck and oropharynx.

(Choices C and D) The submandibular nodes drain the cheeks, lips, gums, and part of the tongue. The submental nodes drain the floor of the mouth and part of the lower lip. These nodes are commonly enlarged with infections affecting the oral cavity, including dental infections and common viral infections (eg, coxsackievirus).

Educational objective:
Lymph node enlargement is most commonly due to infection-triggered cellular proliferation but can be caused by clonal expansion of malignant cells. Enlargement of the supraclavicular lymph nodes, which drain the chest and abdomen, is unlikely to be caused by common childhood infections and is concerning for malignancy.

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A 6-year-old African American male is brought to your office for a routine check-up. His mother remarks that he often seems uninterested in playing with his peers and appears to "run out of breath quickly." His medical records reveal that he has missed several pediatric vaccinations and has been hospitalized twice, once with a "chest infection" and once with abdominal pain. The patient mentions to you that occasionally his "bones hurt." Which of the following protein changes most likely accounts for this patient's condition?

A. Phenylalanine deletion
B. Valine substitution for glutamic acid
C. Phenylalanine substitution for proline
D. Valine substitution for lysine
E. Early termination of polypeptide synthesis

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A. ~~Phenylalanine deletion~~ (2%)
✓ B. Valine substitution for glutamic acid (82%)
C. Phenylalanine substitution for proline (3%)
D. Valine substitution for lysine (9%)
E. Early termination of polypeptide synthesis (2%)

Correct

82%
Answered correctly

45 secs
Time Spent

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This patient is exhibiting signs and symptoms of sickle cell anemia. Sickle cell anemia is a hemoglobinopathy that typically affects patients of African ancestry. A point mutation in the 6th codon of the beta-globin gene, which causes the substitution of valine (hydrophobic) for glutamic acid (hydrophilic), is responsible. The incorporation of this abnormal beta-globin protein into hemoglobin results in the formation of hemoglobin S (HbS). HbS polymerizes at low oxygen tension, causing sickling and hemolysis of erythrocytes and resultant vascular occlusion. This patient's poor exercise tolerance and exertional dyspnea are due to anemia. His history of acute chest syndrome, abdominal pain, and bone pain are due to vaso-occlusive events in the lungs, spleen and bone, respectively.

(Choice A) A phenylalanine deletion (ΔF508) is the most common cause of cystic fibrosis, the most common fatal genetic disease of Caucasians.

(Choice E) Early termination of polypeptide synthesis (nonsense mutation) will produce a truncated protein.

Educational Objective:
Exertional dyspnea, pneumonia resulting in life-threatening acute chest syndrome, and recurrent abdominal and bone pain are clinical features of sickle cell anemia. Sickle cell anemia results from a point mutation

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(Choice A) A phenylalanine deletion (ΔF508) is the most common cause of cystic fibrosis, the most common fatal genetic disease of Caucasians.

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Educational Objective:
Exertional dyspnea, pneumonia resulting in life-threatening acute chest syndrome, and recurrent abdominal and bone pain are clinical features of sickle cell anemia. Sickle cell anemia results from a point mutation that causes valine to substitute for glutamic acid in the sixth position of the b-globin chain of hemoglobin.

Biochemistry	Hematology & Oncology	Sickle cell
Subject	System	Topic

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A 70-year-old female presents to your office complaining of easy fatigability, exertional dyspnea and weight loss. She also complains of frequent falls. Physical examination reveals symmetrically decreased vibratory sensation to the lower extremities. Her hemoglobin is 7.8 g/dL and a peripheral blood smear shows hypersegmented neutrophils. Which of the following is the best treatment for this patient?

A. Iron preparations
B. Vitamin B12
C. Pyridoxine
D. Vitamin C
E. Folic acid
F. Erythropoietin
G. Filgrastim
H. Interleukin-2
I. Antithymocyte globulin

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- A. Iron preparations
- B. Vitamin B12
- C. Pyridoxine
- D. Vitamin C
- E. Folic acid
- F. Erythropoietin
- G. Filgrastim
- H. Interleukin-2
- I. Antithymocyte globulin

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vibratory sensation to the lower extremities. Her hemoglobin is 7.8 g/dL and a peripheral blood smear shows hypersegmented neutrophils. Which of the following is the best treatment for this patient?

- A. Iron preparations (1%)
- ✓ B. Vitamin B12 (90%)
- C. Pyridoxine (1%)
- D. Vitamin C (0%)
- E. Folic acid (3%)
- F. Erythropoietin (1%)
- G. Filgrastim (0%)
- H. Interleukin-2 (0%)
- I. Antithymocyte globulin (0%)

Correct

90%
Answered correctly

38 secs
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Deficiencies of folic acid and vitamin B12 are the most important causes of megaloblastic anemia. Both of these vitamins are required for DNA synthesis in erythropoiesis. When there is a deficiency of either of these vitamins, cell division is delayed, though the cytoplasm develops normally. Thus, the cells enlarge (megaloblasts) but do not divide. The bone marrow is hypercellular in megaloblastic anemia, but the megaloblastic erythroid precursor cells are rapidly destroyed in the bone marrow and few differentiated large RBCs are released into the circulation. In severe megaloblastic anemia, 90% of erythroid precursors are destroyed without ever entering the circulation.

Vitamin B12 and folic acid deficiencies cause similar hematological pictures. However, neurological dysfunction is only seen in patients with vitamin B12 deficiency. This is because B12 deficiency also causes axonal demyelination and degeneration. In late disease, the neurological dysfunction may be irreversible. The main sites of neurological involvement include the peripheral nerves, spinal cord (posterior and lateral columns), and the cerebrum. Decreased vibratory and position sense are early signs of vitamin B12 deficiency. Patients experience ataxia and recurrent falls because of compromised proprioception. Importantly, neurologic abnormalities can occur in vitamin B12 deficiency in the absence of frank anemia. Treating megaloblastic anemia due to vitamin B12 deficiency with folate alone could worsen the neurological dysfunction.

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proprioception. Importantly, neurologic abnormalities can occur in vitamin B12 deficiency in the absence of frank anemia. Treating megaloblastic anemia due to vitamin B12 deficiency with folate alone could worsen the neurological dysfunction.

An RBC mean corpuscular volume (MCV) of more than 100 fL is suggestive of megaloblastic anemia. However, RBC macrocytosis can also occur in liver disease, hypothyroidism, and alcoholic liver disease. MCVs greater than 110 fL are typically seen only with vitamin B12 and folic acid anemias. On peripheral blood smear, there is macrocytosis (large RBCs), hypersegmented neutrophils, and large bizarrely shaped platelets. The presence of even a single neutrophil with more than 6 lobes should raise the suspicion of megaloblastic anemia.

The medications listed in the other answer choices are not used for the treatment of megaloblastic anemia.

Educational Objective:
Vitamin B12 and folic acid deficiencies cause similar hematological pictures. However, neurological dysfunction is only seen in patients with vitamin B12 deficiency. If megaloblastic anemia due to vitamin B12 deficiency is mistakenly treated with folate alone, the neurologic dysfunction can worsen.

Pathology	Hematology & Oncology	Anemia
Subject	System	Topic

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A 34-year-old man with an unremarkable past medical history is evaluated for an enlarged lymph node in his anterior cervical chain that measures 4 cm in diameter. The patient first felt the lymph node several weeks ago and states that it has been steadily increasing in size. He is concerned about whether or not he "has cancer." The patient is referred to a specialist for surgical removal of the enlarged node. Biopsy reveals abnormal lymph node architecture and numerous lymphocytes. Which of the following, if present, would be most consistent with malignancy in this patient?

A. Lymphocyte pleomorphism
B. Abundant mitotic figures within the lymph node
C. Nuclear changes in lymphocytes
D. Monoclonal T-cell receptor gene rearrangements
E. Admixture of several lymphoid cell types within the lymph node

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A. Lymphocyte pleomorphism (12%)
B. Abundant mitotic figures within the lymph node (32%)
C. Nuclear changes in lymphocytes (14%)
D. Monoclonal T-cell receptor gene rearrangements (34%)
E. Admixture of several lymphoid cell types within the lymph node (5%)

Correct

34%
Answered correctly

20 secs
Time Spent

11/15/2020
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Lymphadenopathy can represent inflammatory changes within the lymph node (reactive hyperplasia) or malignant transformation. Reactive hyperplasia is a broad term that encompasses all benign, reversible enlargement of the lymphoid tissue secondary to an antigenic stimulus. The nodal response to antigenic stimuli is highly variable and can be classified as follicular hyperplasia, sinus hyperplasia, or diffuse hyperplasia. Follicular hyperplasia occurs when the follicles increase in size and number, whereas sinus hyperplasia occurs when the sinuses enlarge and fill with histiocytes. Diffuse hyperplasia is observed when the nodal architecture is diffusely effaced by sheets of lymphocytes, immunoblasts, and macrophages. When malignant transformation occurs (as in lymphomas), the normal lymph node architecture is distorted or effaced by the proliferation of malignant lymphoid cells, often to a greater extent than that seen with reactive hyperplasia. Malignancy-associated effacement of nodal architecture may be follicular or diffuse.

Reactive lymphoid hyperplasia is polyclonal in that it consists of a proliferation of many different cell types within the lymph node. For each type of lymphocyte responding to an antigenic stimulus, multiple genetically-distinct cells of that variety undergo limited monoclonal expansion, leading to an overall polyclonal response. Malignant transformation, in contrast, is monoclonal in that it results from the unchecked proliferation of a single genetically unique cell from only one cell line.

Evaluation for monoclonality of the lymphocyte population is important when lymphoma is suspected. The clonality of a T-cell population is assessed by molecular methods, such as PCR, that examine the

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genetically-distinct cells of that variety undergo limited monoclonal expansion, leading to an overall polyclonal response. Malignant transformation, in contrast, is monoclonal in that it results from the unchecked proliferation of a single genetically unique cell from only one cell line.

Evaluation for monoclonality of the lymphocyte population is important when lymphoma is suspected. The clonality of a T-cell population is assessed by molecular methods, such as PCR, that examine the rearrangement of T-cell receptor (TCR) genes. If a single allele for the V region of the T-cell receptor predominates in a lymphocytic population, monoclonal proliferation is suspected. The same principle applies when assessing B-cell clonality. Monoclonal rearrangement of the genes for immunoglobulin variable regions is suggestive of a B-cell lymphoma. Of the choices given, monoclonal TCR gene rearrangement is most indicative of malignant processes, especially in the context of appropriate clinical features (i.e., weight loss, night sweats, fever, anorexia).

(Choices A, B, & C) Pleomorphism, increased mitoses, and nuclear changes are all commonly seen in the lymphocytes of a reactive hyperplastic lymph node. These findings do not automatically classify the specimen as malignant.

(Choice E) An admixture of several lymphoid cell types in a lymph node is suggestive of a benign process. A predominantly monomorphic cell population is indicative of malignancy and is characteristic of

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features (i.e., weight loss, night sweats, fever, anorexia).

(Choices A, B, & C) Pleomorphism, increased mitoses, and nuclear changes are all commonly seen in the lymphocytes of a reactive hyperplastic lymph node. These findings do not automatically classify the specimen as malignant.

(Choice E) An admixture of several lymphoid cell types in a lymph node is suggestive of a benign process. A predominantly monomorphic cell population is indicative of malignancy and is characteristic of non-Hodgkin's lymphoma. Hodgkin's lymphoma does demonstrate an admixture of several lymphoid cell types within the lymph nodes; however, this finding does not distinguish Hodgkin's lymphoma from reactive hyperplasia. Additionally, genetic analysis of Reed-Sternberg cells most often reveals monoclonal characteristics.

Educational objective:
Benign lymph node enlargement in response to antigenic stimulation is associated with a polyclonal proliferation of lymphocytes. A monoclonal lymphocytic proliferation is strong evidence of malignancy.

References

- Resolving T-cell receptor clonality in two and genotype in four multiplex polymerase chain reactions.
- The polymerase chain reaction in the demonstration of monoclonality in T cell lymphomas.

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www.ncbi.nlm.nih.gov/pubmed/16266900

A 35-year-old woman comes to the physician complaining of weakness, fatigue, and pallor. She denies heavy menses or melena. Physical examination is unremarkable except for conjunctival pallor. Laboratory results are as follows:

Complete blood count	
Hemoglobin	7.2 g/dL
Erythrocyte count	1.8 million/μL
Mean corpuscular volume	90 fL
Reticulocytes	0.1%
Platelets	280,000 /μL
Leukocyte count	6,700 cells/μL

Iron studies and serum B_{12} and folic acid levels are within normal limits. Bone marrow biopsy shows

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Platelets	280,000 /μL
Leukocyte count	6,700 cells/μL

Iron studies and serum B_{12} and folic acid levels are within normal limits. Bone marrow biopsy shows absence of erythroid precursors but preserved myeloid and megakaryocytic elements. Further workup would most likely show which of the following?

A. Hepatocellular carcinoma
B. Renal cell carcinoma
C. Thymic tumor
D. Cerebellar hemangioblastoma
E. Uterine fibroid

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Platelets	280,000 /µL
Leukocyte count	6,700 cells/µL

Iron studies and serum B_{12} and folic acid levels are within normal limits. Bone marrow biopsy shows absence of erythroid precursors but preserved myeloid and megakaryocytic elements. Further workup would most likely show which of the following?

- A. Hepatocellular carcinoma (10%)
- B. Renal cell carcinoma (53%) ✗
- C. Thymic tumor (23%) ✓
- D. Cerebellar hemangioblastoma (6%)
- E. Uterine fibroid (5%)

Incorrect
Correct answer

23%
Answered correctly

58 secs
Time Spent

08/30/2020
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This patient's pallor and fatigue suggest that she is suffering from anemia, which is confirmed by her low erythrocyte count, low percentage of reticulocytes (decreased RBC production), and low hemoglobin. Importantly, her white blood cell and platelet counts are within normal limits and their bone marrow precursors appear normal as well. The most likely diagnosis is pure red cell aplasia (PRCA), a rare form of marrow failure characterized by severe hypoplasia of marrow erythroid elements in the setting of normal granulopoiesis and thrombopoiesis.

The pathogenesis of PRCA often involves the inhibition of erythropoietic precursors and progenitors by IgG autoantibodies or cytotoxic T lymphocytes. It has been associated with immune system diseases such as thymomas and lymphocytic leukemias. When a thymoma is present, removal can occasionally cure PRCA. Thus, all patients with PRCA should undergo a chest CT scan. PRCA can also result from parvovirus B19 infection. This virus preferentially attacks and destroys proerythroblasts. Recent parvovirus infection can be confirmed via the detection of anti-B19 IgM antibodies in the serum.

(Choice A) Hepatocellular carcinoma (HCC) can cause anemia of chronic disease, in which the total iron binding capacity is low. However, this patient's iron studies are within normal limits. HCC tumors may also secrete erythropoietin, although polycythemia is less common.

(Choice B) Renal cell carcinoma (RCC) can cause both anemia of chronic disease and iron deficiency

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(Choice B) Renal cell carcinoma (RCC) can cause both anemia of chronic disease and iron deficiency anemia due to chronic hematuria. Some renal cell tumors can produce erythropoietin and cause polycythemia. Thus, anemia, polycythemia, or normal hemoglobin may be present in the setting of RCC. However, selective absence of erythroid precursors in the bone marrow would not occur with RCC. In addition, RCC is rare in younger patients, whereas benign thymomas are more common.

(Choice D) Cerebellar hemangioblastomas can produce erythropoietin and are often associated with polycythemia.

(Choice E) Uterine fibroids can cause bleeding and may result in microcytic hypochromic anemia with iron studies showing low iron and increased total iron binding capacity. However, fibroids can also produce erythropoietin and can cause polycythemia.

Educational objective:
Pure red cell aplasia is a rare form of marrow failure characterized by severe hypoplasia of marrow erythroid elements in the setting of normal granulopoiesis and thrombopoiesis. Pure red cell aplasia is associated with thymoma, lymphocytic leukemias, and parvovirus B19 infection.

Pathology	Hematology & Oncology	Pure red cell aplasia
Subject	System	Topic

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Cancer cells from a 23-year-old male with testicular cancer demonstrate high sensitivity to etoposide. The etoposide-killed cancer cells show a high number of double-stranded DNA fractures. These fractures are due to dysfunction of which of the following?

A. Thymidylate synthase
B. Topoisomerase I
C. Topoisomerase II
D. Microtubules
E. Dihydrofolate reductase

Submit

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Cancer cells from a 23-year-old male with testicular cancer demonstrate high sensitivity to etoposide. The etoposide-killed cancer cells show a high number of double-stranded DNA fractures. These fractures are due to dysfunction of which of the following?

- A. ~~Thymidylate synthase~~ (5%)
- B. Topoisomerase I (18%)
- ✓ C. Topoisomerase II (66%)
- D. ~~Microtubules~~ (6%)
- E. ~~Dihydrofolate reductase~~ (2%)

Correct

66% Answered correctly

26 secs Time Spent

01/30/2021 Last Updated

Explanation

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Etoposide is a semisynthetic derivative of the plant alkaloid podophyllotoxin, which targets topoisomerase II. The topoisomerases are enzymes that relieve the DNA supercoiling that occurs during DNA replication as a result of separation and unwinding of the double helix. Topoisomerase I makes single-stranded nicks to relieve negative supercoiling, while topoisomerase II induces transient breaks in both DNA strands simultaneously to relieve both positive and negative supercoiling. Etoposide and podophyllin specifically inhibit topoisomerase II's ability to seal the strand breaks it induces, causing chromosomal breaks to accumulate and eventual cell death. Two major uses of etoposide are in testicular cancer and small cell lung cancer. Podophyllin is used topically to treat genital warts.

(Choices A and E) Antimetabolites are medications that interfere with nucleotide metabolism, thus inhibiting incorporation of new nucleotides into elongating DNA strands. For example, thymidylate synthase and dihydrofolate reductase are enzymes central to thymidine nucleotide synthesis. 5-Fluorouracil and 5-deoxyuridine are antimetabolites that inhibit thymidylate synthase, and methotrexate is an antimetabolite that inhibits dihydrofolate reductase.

(Choice B) Irinotecan and topotecan inhibit topoisomerase I, an enzyme that induces single-strand breaks in DNA to relieve negative supercoiling during replication.

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(Choice B) Irinotecan and topotecan inhibit topoisomerase I, an enzyme that induces single-strand breaks in DNA to relieve negative supercoiling during replication.

(Choice D) Vinca alkaloids like vincristine and vinblastine bind tubulin monomers, disrupting the microtubules necessary for separating chromosome strands during mitosis. Taxanes like paclitaxel also cause microtubular dysfunction.

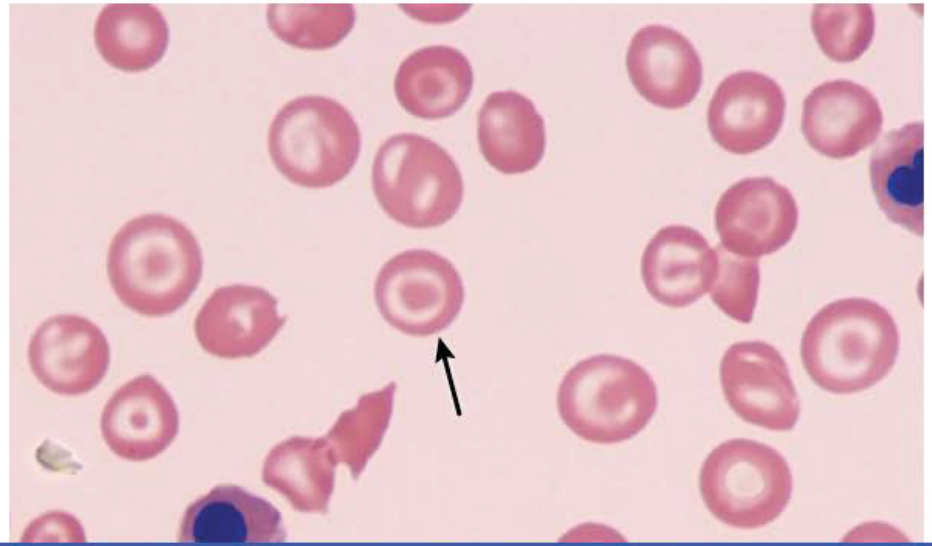
Educational Objective:
Etoposide is a chemotherapeutic agent that inhibits the sealing activity of topoisomerase II. Treatment with etoposide causes chromosomal breaks to accumulate in dividing cells, ultimately causing cell death.

Pharmacology	Hematology & Oncology	Chemotherapy
Subject	System	Topic

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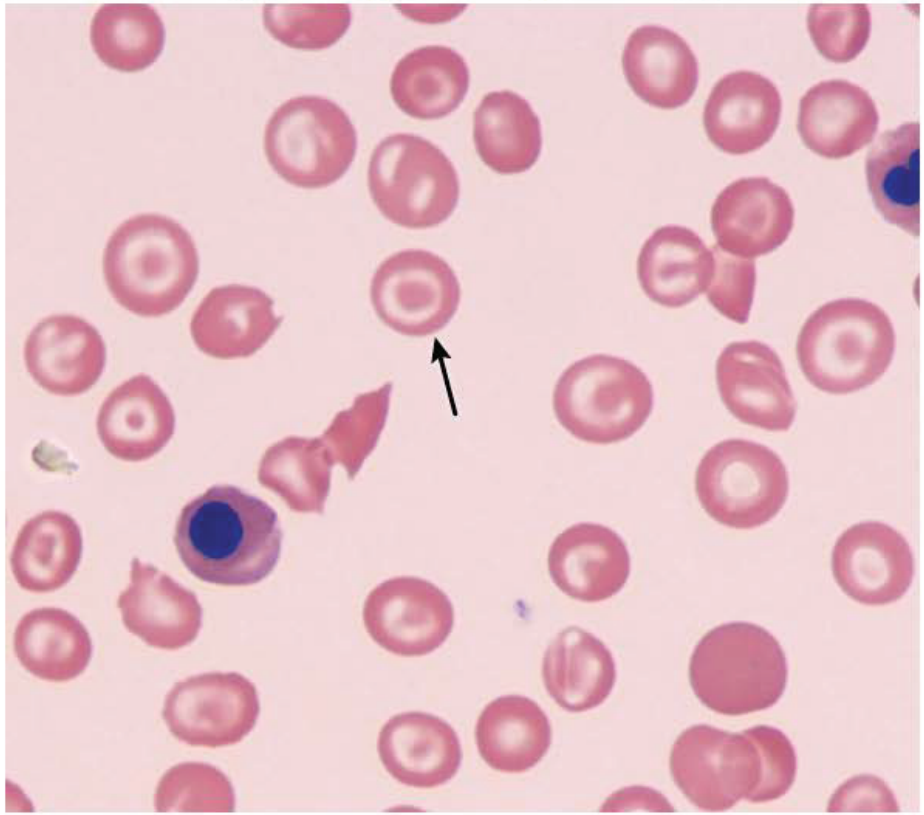
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A 26-year-old woman comes to the office for a follow-up appointment. She has a history of immune thrombocytopenia that failed to improve with glucocorticoid therapy. The patient underwent splenectomy 6 months ago, which resulted in improved platelet counts. She received the recommended vaccinations after her surgery and currently feels well. Physical examination shows no abnormalities. A peripheral blood smear reveals many red blood cells of a specific morphology as indicated by the arrow below.



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An increase in which of the following features best explains the presence of these abnormal cells?

A. Aggregated iron deposits
B. Clusters of remnant DNA
C. Denatured hemoglobin
D. Fragility to osmotic stress
E. Precipitated ribosomes
F. Surface area-to-volume ratio

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An increase in which of the following features best explains the presence of these abnormal cells?

A. Aggregated iron deposits (2%)
B. Clusters of remnant DNA (7%)
C. Denatured hemoglobin (16%)
D. Fragility to osmotic stress (8%)
E. Precipitated ribosomes (2%)
F. Surface area-to-volume ratio (62%)

Correct
62%
49 secs
10/20/2020

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Target cells are red blood cells with a dark center, a surrounding halo of pallor, and a dark peripheral ring. They form in erythrocytes with an **excessive surface area-to-volume ratio**, which results in redundant erythrocyte cell membrane folding upon itself (thereby creating the appearance of a target). Target cells occur in the following conditions:

- Reduced erythrocyte cell volume from deficient hemoglobin synthesis (eg, thalassemia, iron deficiency) or structural mutations to hemoglobin (eg, sickle cell)
- **Excessive erythrocyte cellular membrane** due to greater cholesterol-to-phospholipid ratios (eg, obstructive liver disease) or **splenectomy**

Macrophages in the red pulp of the spleen remove excess membrane from red cells, a process called "**splenic conditioning**." Patients who undergo splenectomy are **unable to prune** erythrocytes and generally develop target cells a few weeks following the procedure. However, over time, macrophages in nonsplenic tissue (eg, liver) take up the task of pruning erythrocytes, which typically eliminates (or diminishes) the presence of target cells in the circulation.

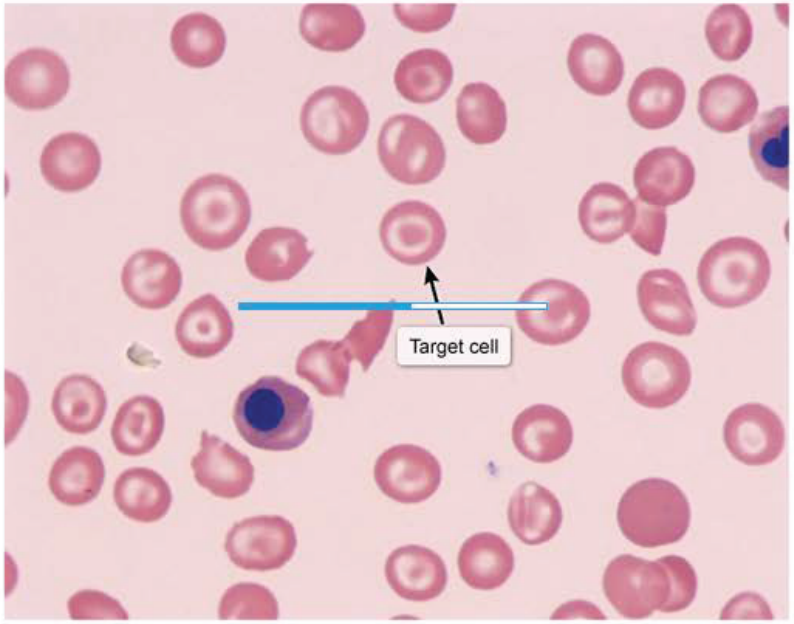
(Choice A) Pappenheimer bodies are aggregated iron deposits in erythrocytes that are often seen in patients with sideroblastic anemia. They appear as dark blue inclusions.

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Exhibit Display

Target cells



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(Choice A) Pappenheimer bodies are aggregated iron deposits in erythrocytes that are often seen in patients with sideroblastic anemia. They appear as dark blue inclusions.

(Choice B) Howell-Jolly bodies are clusters of DNA remnants in erythrocytes due to hyposplenism or asplenism (the spleen usually removes the DNA remnants). They appear as peripheral, round, dark purple, blue, or red inclusions.

(Choice C) Heinz bodies are aggregates of denatured hemoglobin that may be present in erythrocytes when patients have glucose-6-phosphate dehydrogenase deficiency or thalassemia. They cannot be seen on routine staining.

(Choice D) Spherocytes have low surface area-to-volume ratios and are more susceptible to osmotic stress. They are seen most commonly in hemolytic anemia and hereditary spherocytosis and appear as dense, round red blood cells. Target cells are less susceptible to osmotic stress than normal red blood cells or spherocytes due to their excess membrane.

(Choice E) Basophilic stippling is blue granules dispersed within the cytosol of erythrocytes due to precipitated ribosomes. It is seen most commonly in thalassemias, alcohol use disorder, and lead/heavy metal poisoning.

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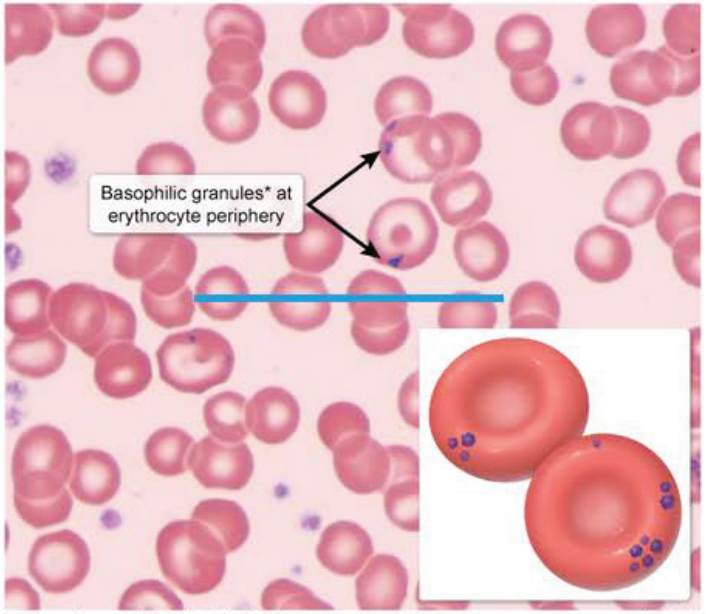
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Exhibit Display

Pappenheimer bodies



*Iron granules associated with sideroblastic anemia

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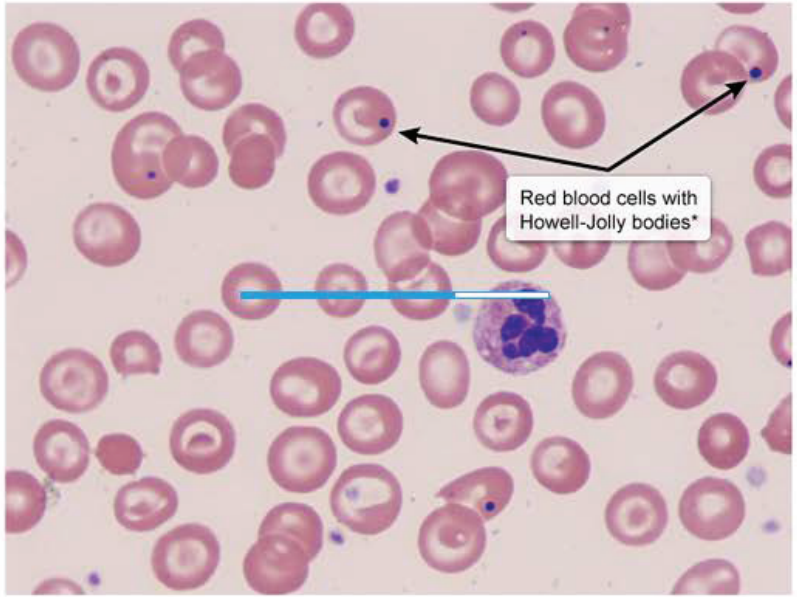
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Howell-Jolly bodies



*Nuclear remnants seen with asplenism or hyposplenism

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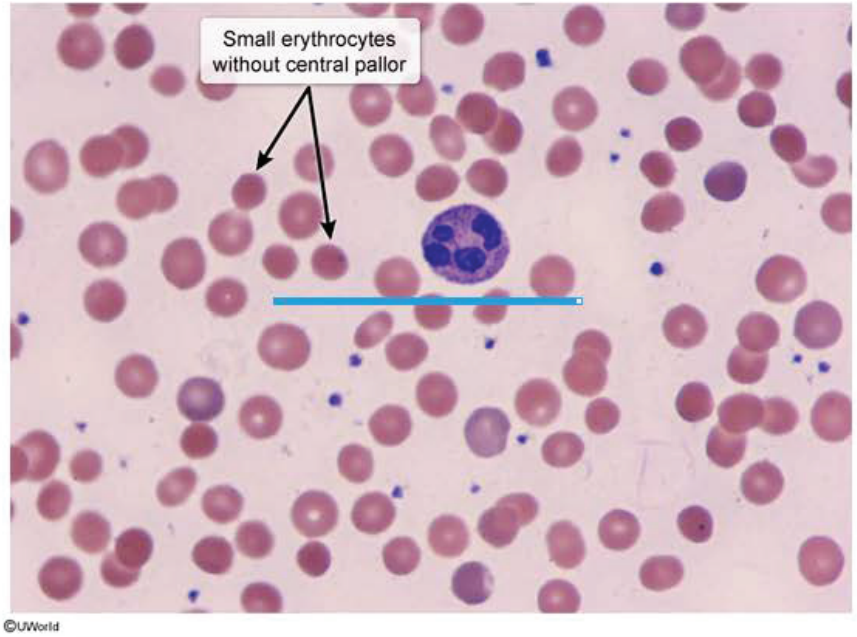
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Spherocytes



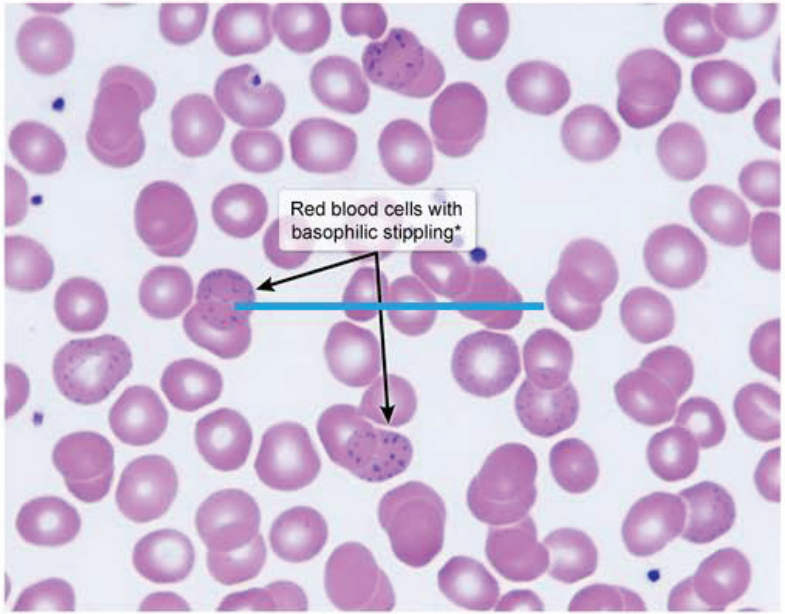
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Basophilic stippling



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on routine staining.

(Choice D) Spherocytes have low surface area-to-volume ratios and are more susceptible to osmotic stress. They are seen most commonly in hemolytic anemia and hereditary spherocytosis and appear as dense, round red blood cells. Target cells are less susceptible to osmotic stress than normal red blood cells or spherocytes due to their excess membrane.

(Choice E) Basophilic stippling is blue granules dispersed within the cytosol of erythrocytes due to precipitated ribosomes. It is seen most commonly in thalassemias, alcohol use disorder, and lead/heavy metal poisoning.

Educational objective:

Target cells form when erythrocytes have reduced cell volume (eg, thalassemia, iron deficiency) or excessive membrane (eg, obstructive liver disease, postsplenectomy). Patients who undergo splenectomy usually develop target cells because the spleen is the primary organ that prunes excessive red cell membrane.

Pathophysiology	Hematology & Oncology	Splenectomy
Subject	System	Topic

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A 12-year-old African American male is brought to the emergency room with high fever, chest pains, and dyspnea. His past medical history is significant for two prior hospitalizations for abdominal pain, which resolved with analgesics and hydration. Evaluation today reveals a hematocrit of 23% and reticulocyte count of 9%. Several hours after being admitted, the patient dies in the hospital. At autopsy, the patient's spleen is firm and brown; this finding is most likely related to:

A. ~~Work hypertrophy~~ (17%)
B. ~~Follicular hyperplasia~~ (2%)
C. Vascular occlusion (73%)
D. Pressure atrophy (4%)
E. Dysplasia (0%)
F. Lipid accumulation (1%)

Correct

73% Answered correctly
47 secs Time Spent
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In an African American patient with the hematologic findings described above and recurrent episodes of abdominal pain that resolve with hydration, sickle cell anemia is the most likely diagnosis. Today this patient has presented with symptoms of "acute chest syndrome" (ACS), which is vaso-occlusive crisis localized to the pulmonary vasculature that can occur in patients with sickle cell anemia. ACS is commonly precipitated by pulmonary infection.

In patients with homozygous hemoglobin S disease, vaso-occlusive crises can also cause splenic infarctions. Repeated infarctions over time produce a spleen that is shrunken, discolored, and fibrotic. By the time they reach adulthood, most patients with sickle cell anemia have undergone "autosplenectomy" as a result of these infarcts and are left with only a small, scarred splenic remnant. The spleen may demonstrate brownish discoloration (hemosiderosis) due to extensive ingestion of sickled RBCs by splenic macrophages (extravascular hemolysis).

(Choices A and B) There may be hyperplasia and hypertrophy of normal splenic elements (especially macrophages and lymphoid cells) in systemic infections and various other disease states.

(Choice D) Pressure atrophy of the splenic parenchyma can be seen when there is a tumor infiltrating the spleen.

(Choice E) Dysplasia is disordered growth and/or abnormal hyperplasia of epithelia. This term is rarely

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macrophages (extravascular hemolysis).

(Choices A and B) There may be hyperplasia and hypertrophy of normal splenic elements (especially macrophages and lymphoid cells) in systemic infections and various other disease states.

(Choice D) Pressure atrophy of the splenic parenchyma can be seen when there is a tumor infiltrating the spleen.

(Choice E) Dysplasia is disordered growth and/or abnormal hyperplasia of epithelia. This term is rarely applied to histologic components of the spleen.

(Choice F) Intrasplenic lipid accumulation might be seen in lysosomal lipid storage disorders like Gaucher's disease.

Educational Objective:
The major chronic pathologic changes in the spleens of patients with sickle cell anemia result from repetitive splenic infarctions caused by splenic microvessel occlusion. Fibrosis, brownish discoloration, and eventual autosplenectomy ultimately result.

Pathology	Hematology & Oncology	Sickle cell
Subject	System	Topic

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A 68-year-old man comes to the emergency department due to lightheadedness, generalized weakness, and palpitations. The patient has a prolonged history of hypertension and takes amlodipine. He does not use tobacco or alcohol. His blood pressure is 110/60 mm Hg and pulse is 144/min and irregular. ECG shows an irregularly irregular rhythm and absent P waves. The patient is started on beta blocker therapy for rate control, with improvement in his heart rate. Long-term anticoagulation is initiated to prevent atrial thrombus formation, and he is eventually discharged home on warfarin. Which of the following is the best test to monitor the anticoagulation effect of warfarin in this patient?

A. Activated partial thromboplastin time
B. Bleeding time
C. Fibrin split products
D. Fibrinogen levels
E. Prothrombin time

Submit

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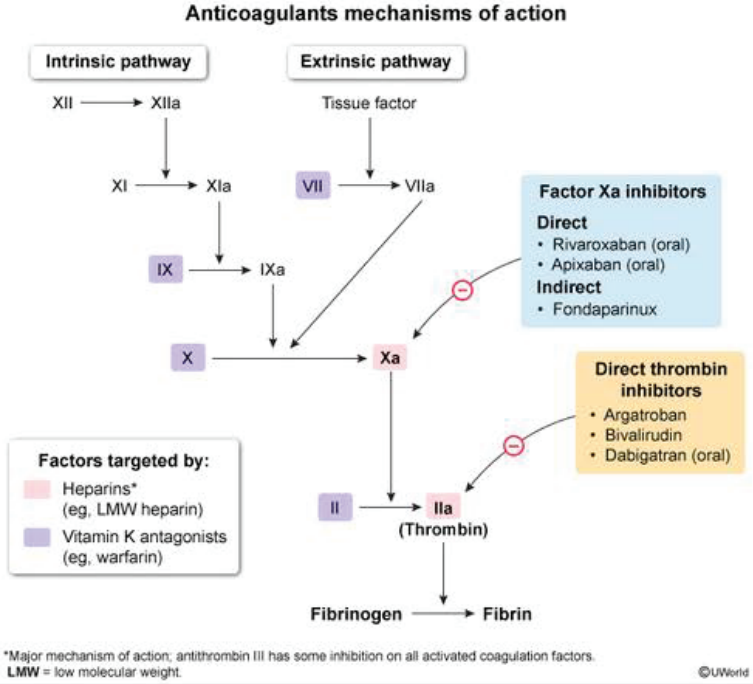
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A. Activated partial thromboplastin time (12%)
B. Bleeding time (2%)
C. Fibrin split products (1%)
D. Fibrinogen levels (0%)
✓ E. Prothrombin time (83%)

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This patient's ECG (irregularly irregular rhythm with absent P waves) suggests **atrial fibrillation (AF)**, which alters cardiac flow dynamics, making thrombus formation more common. If this thrombus detaches from the atrial wall, there is a risk of stroke. The oral anticoagulant **warfarin** (Coumadin) reduces thrombus formation risk by inhibiting the activation of vitamin K-dependent clotting factors II, VII, IX, and X **(vitamin K antagonist)**. This leads to decreased levels of these factors, particularly **factor VII**, and therefore prolongs the prothrombin time (PT). Another useful laboratory value is the **International Normalized Ratio (INR)**, a ratio of the patient's PT to a control (usual INR target for AF: 2.0-3.0). Examples of indications include AF, deep venous thrombosis, and pulmonary thromboembolism. Outpatients who take warfarin typically have their INR checked every few weeks (more frequently initially).

The most common side effect is excessive anticoagulation leading to bleeding (which can require vitamin K and fresh frozen plasma if rapid reversal is needed). Skin necrosis can occur during the first few days of treatment due to a transient hypercoagulable state (reduction in protein C anticoagulant activity before affecting other factors' procoagulant activity); for this reason, heparin is typically administered temporarily at the start of warfarin therapy ("heparin bridge"). Warfarin should not be used during pregnancy because it is teratogenic and can cause fetal bleeding.

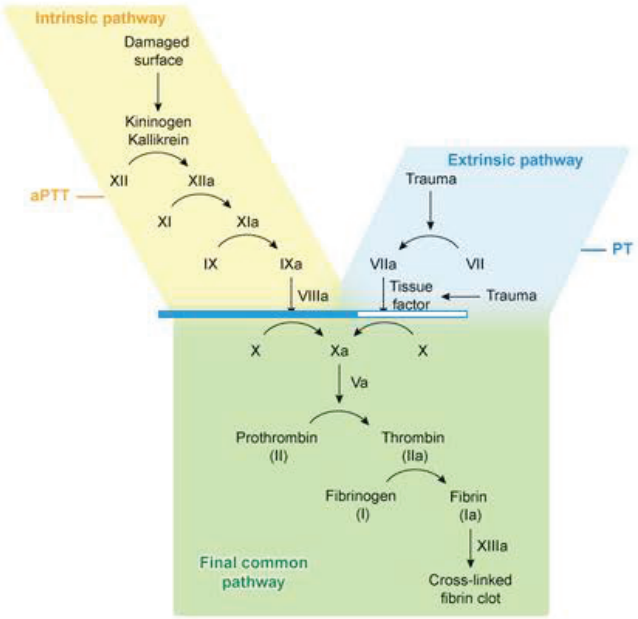
(Choice A) Activated partial thromboplastin time (aPTT) is used to monitor unfractionated heparin, which

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Exhibit Display

Coagulation cascade pathway



aPTT = activated partial thromboplastin time; PT = prothrombin time.

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the start of warfarin therapy ("heparin bridge"). Warfarin should not be used during pregnancy because it is teratogenic and can cause fetal bleeding.

(Choice A) Activated partial thromboplastin time (aPTT) is used to monitor unfractionated heparin, which primarily affects the intrinsic coagulation pathway.

(Choice B) Bleeding time is used for the assessment of platelet function. Increased bleeding time can be seen with thrombocytopenia, von Willebrand disease, defects of platelet aggregation, disseminated intravascular coagulation (DIC), and aspirin therapy.

(Choices C and D) The combination of a decreased fibrinogen level and the presence of fibrin split products (such as D-dimer) is characteristic of DIC.

Educational objective:
Warfarin is an oral anticoagulant that inhibits the carboxylation of vitamin K-dependent coagulation factors II, VII, IX, and X. It is used in atrial fibrillation, deep venous thrombosis, and pulmonary thromboembolism. Prothrombin time (PT)/International Normalized Ratio (INR) should be monitored regularly during treatment with warfarin. Activated partial thromboplastin time (aPTT) is used for monitoring unfractionated heparin.

Pharmacology	Hematology & Oncology	Anticoagulants
Subject	System	Topic

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A 64-year-old man comes to the office due to 3 months of constant, dull, low back pain that is worse with movement. The patient has also had intermittent episodes of difficulty urinating over the last year. He has no other medical conditions and takes no medications. The patient smoked a pack of cigarettes daily for 15 years but quit 10 years ago. Vital signs are within normal limits. On physical examination, the lungs are clear and heart sounds are normal. The abdomen is soft and nontender with no hepatosplenomegaly. Digital rectal examination shows a diffusely enlarged prostate with no nodules. Laboratory testing reveals a serum creatinine level of 1.9 mg/dL. Urine dipstick testing is negative, but 24-hour urinary protein excretion is elevated. Urine microscopy shows waxy, laminated casts. Imaging of the spine demonstrates diffuse osteopenia and multiple irregular, radiolucent lesions in the thoracic and lumbar vertebrae. Biopsy from one of the bone lesions is most likely to reveal which of the following histopathological findings?

A. Branching papillae lined by cuboidal cells with overlapping nuclei

B. Infiltrating glandular cells with substantial adjacent osteoblasts

C. Large, malignant cells containing keratin and intercellular bridges

D. Clusters of mature plasma cells and plasmablasts

E. Sheets of round or polygonal cells with abundant clear cytoplasm

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A. Branching papillae lined by cuboidal cells with overlapping nuclei
B. Infiltrating glandular cells with substantial adjacent osteoblasts
C. Large, malignant cells containing keratin and intercellular bridges
D. Clusters of mature plasma cells and plasmablasts
E. Sheets of round or polygonal cells with abundant clear cytoplasm

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A. Branching papillae lined by cuboidal cells with overlapping nuclei (3%)

B. Infiltrating glandular cells with substantial adjacent osteoblasts (21%)

C. Large, malignant cells containing keratin and intercellular bridges (7%)

D. Clusters of mature plasma cells and plasmablasts (55%)

E. Sheets of round or polygonal cells with abundant clear cytoplasm (12%)

Incorrect
Correct answer

55%

01 min, 15 secs

11/29/2020

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Explanation

Multiple myeloma	
Pathophysiology	• Plasma cell neoplasm produces **monoclonal** paraprotein (immunoglobulin)
Manifestations	• Bone pain, fractures • Constitutional symptoms (weight loss, fatigue) • Recurrent infections
Laboratory	• Normocytic anemia • Renal insufficiency • Hypercalcemia (constipation, muscle weakness) • Monoclonal paraproteinemia **(M-spike)**
Radiology	• **Osteolytic lesions**/osteopenia (osteoclast activation)

This older patient with back pain has several irregularly-shaped vertebral lesions, raising strong suspicion for metastatic disease. Differentiation of the underlying tumor is often assisted by whether the lesion is

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This older patient with back pain has several irregularly-shaped vertebral lesions, raising strong suspicion for metastatic disease. Differentiation of the underlying tumor is often assisted by whether the lesion is sclerotic (osteoblastic) or radiolucent (osteolytic). **Multiple myeloma**, a clonal plasma cell malignancy, is one of the most common causes of **radiolucent bone lesions** in adults; the tumor multiplies in the bone marrow and generates osteolytic cytokines, causing bone pain, bone destruction, pathologic fractures, and hypercalcemia.

Myeloma cells also produce excessive **monoclonal immunoglobulin** (paraprotein) that can clog the renal tubules and subsequently cause **light-chain cast nephropathy**. This is typically characterized by **mild renal insufficiency**, normal urine dipstick for protein (this test detects albumin only), elevated 24-hour urine protein (this test detects light-chain proteins), and waxy, laminated casts. Excessive light chains can also form fibrils and deposit in tissues, leading to amyloid light-chain amyloidosis. Monoclonal immunoglobulins are identified by urine or serum protein electrophoresis (M-spike).

The diagnosis of myeloma is confirmed by bone marrow aspirate or biopsy, which will demonstrate >10% plasma cells. Plasma cells are identified based upon "clock-face" chromatin, abundant basophilic cytoplasm, and prominent perinuclear clear areas (Golgi apparatus).

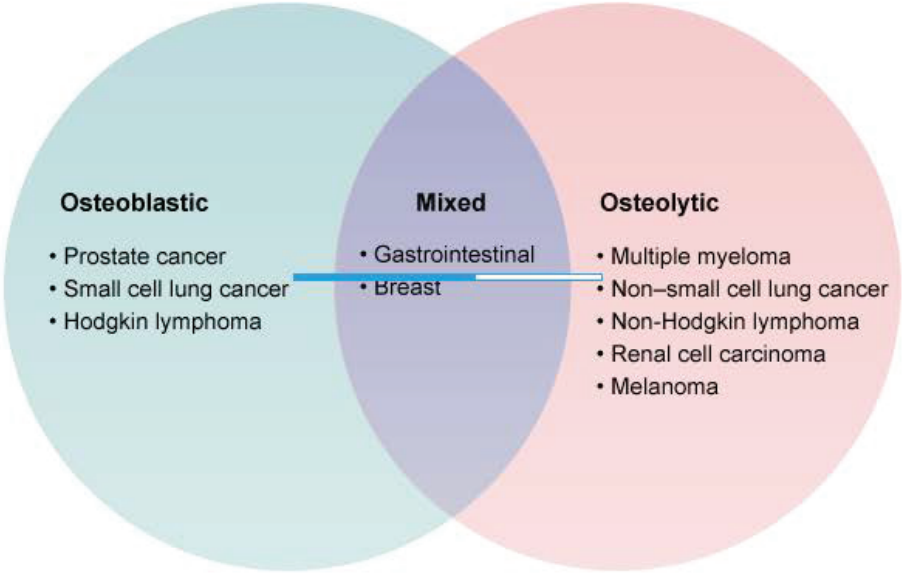
(Choice A) Papillary thyroid cancer is characterized by branching papillae lined by cuboidal cells with

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Exhibit Display

Bone metastases



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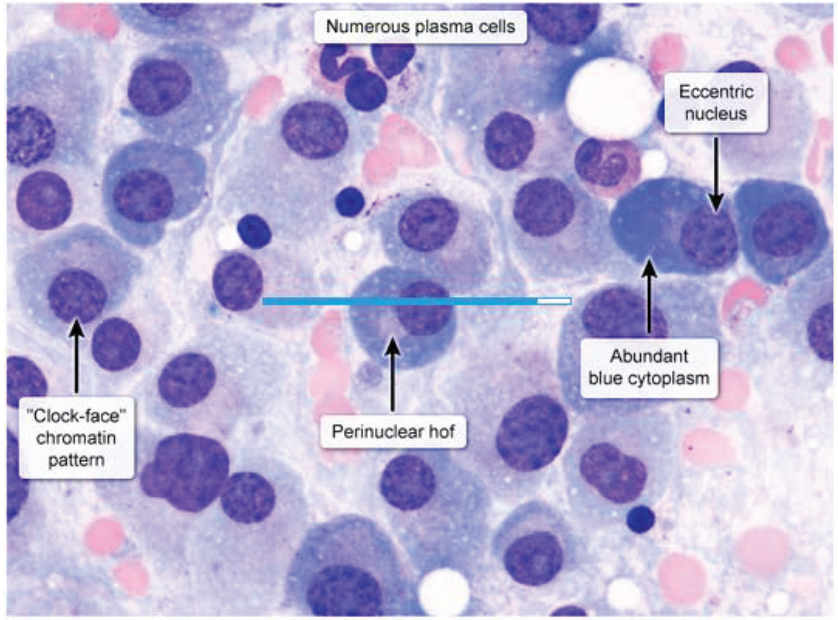
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Exhibit Display

Multiple myeloma



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(Choice A) Papillary thyroid cancer is characterized by branching papillae lined by cuboidal cells with overlying nuclei (often with calcified psammoma bodies). Most cases progress slowly and present with a thyroid mass that may invade adjacent structures; bone lesions are relatively uncommon.

(Choice B) Prostate adenocarcinoma is a glandular tumor that often spreads to the bones; however, it generates sclerotic (osteoblastic) bone lesions, not radiolucent bone lesions. Prostate cancer does not generally impinge on the urethra (no urinary symptoms) and is usually associated with a nodule on prostate examination. This patient's intermittent difficulty urinating and diffusely enlarged prostate with no nodules likely indicate benign prostatic hyperplasia.

(Choices C and E) Squamous cell lung cancer is associated with large, malignant cells containing keratin with intercellular bridges. Renal cell carcinoma is associated with sheets of round or polygonal cells with abundant clear cytoplasm. Although both tumors commonly form osteolytic lesions in the spine, neither regularly cause renal insufficiency, elevated urine protein, and waxy urinary casts.

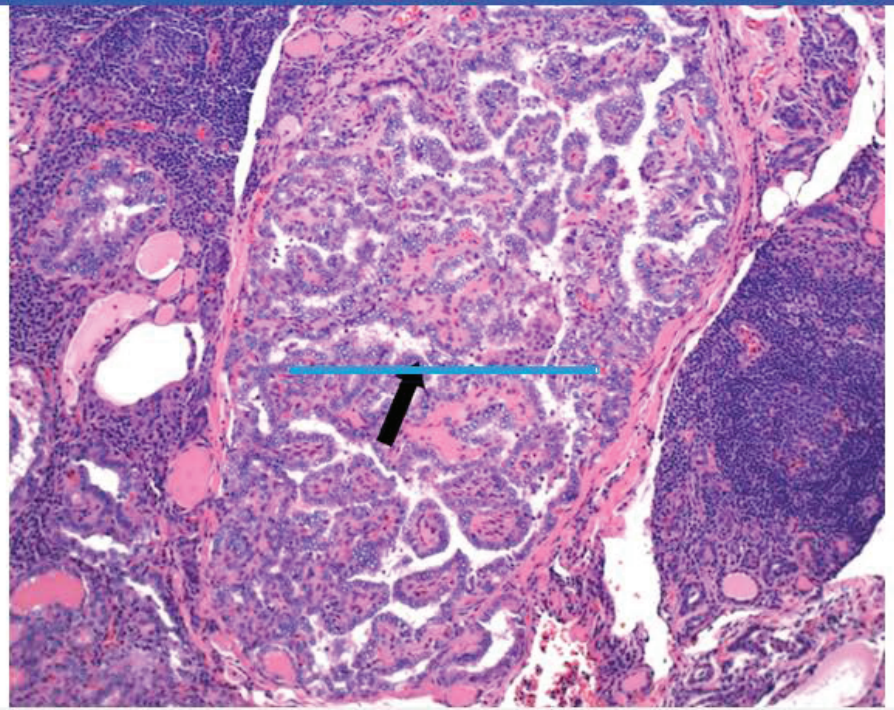
Educational objective:
Multiple myeloma is a plasma cell malignancy that replicates in the bone marrow and causes osteolytic bone lesions, bone destruction, hypercalcemia, and pathologic fractures. Histopathology will show replacement of the normal bone marrow with plasma cells and blasts.

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(Choice A) Papillary thyroid cancer is characterized by branching papillae lined by cuboidal cells with

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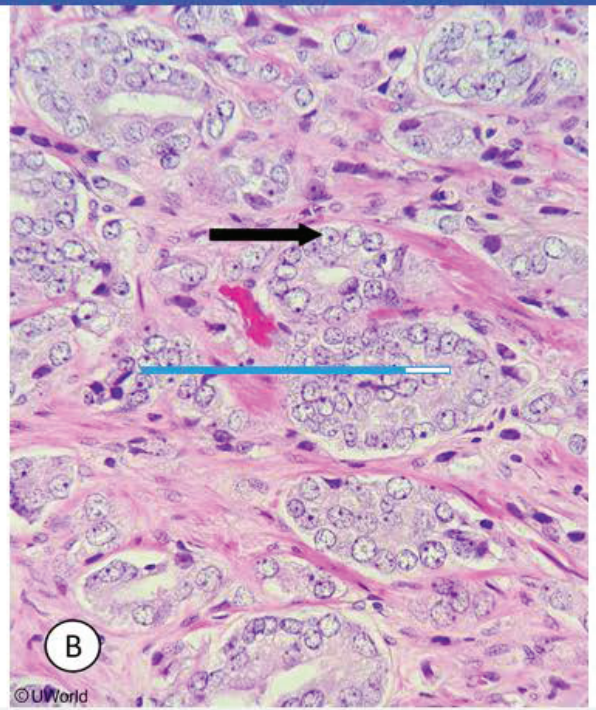
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(Choice A) Papillary thyroid cancer is characterized by branching papillae lined by cuboidal cells with

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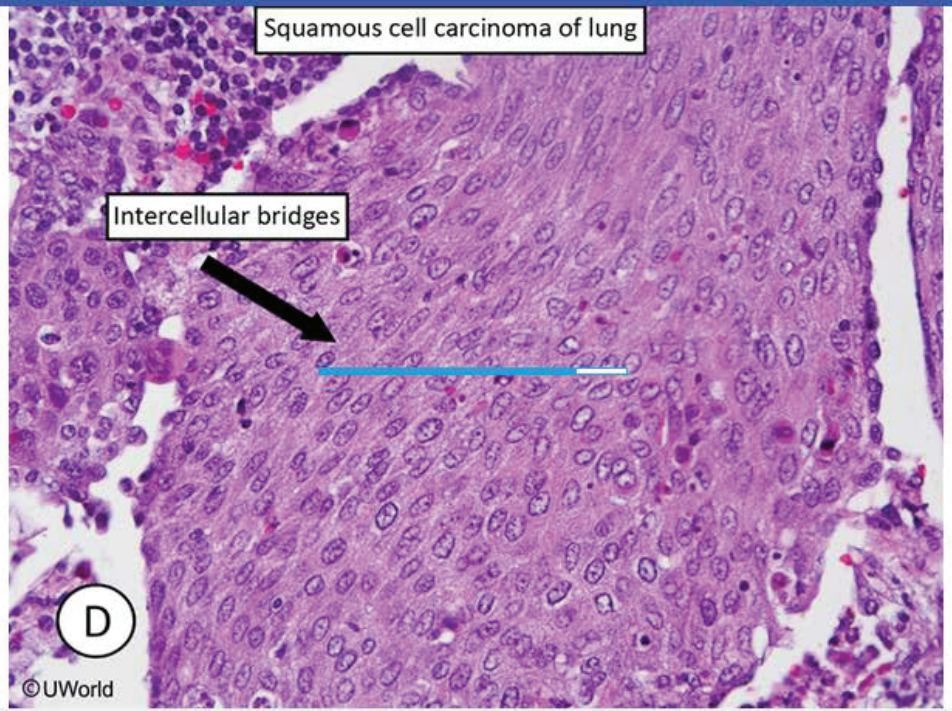
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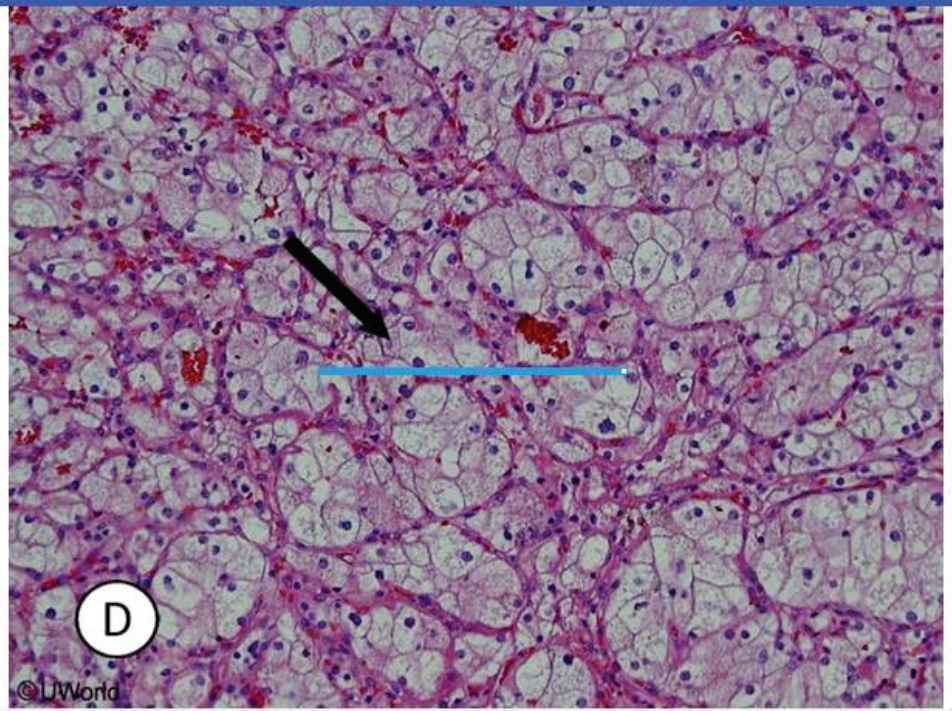
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(Choice A) Papillary thyroid cancer is characterized by branching papillae lined by cuboidal cells with

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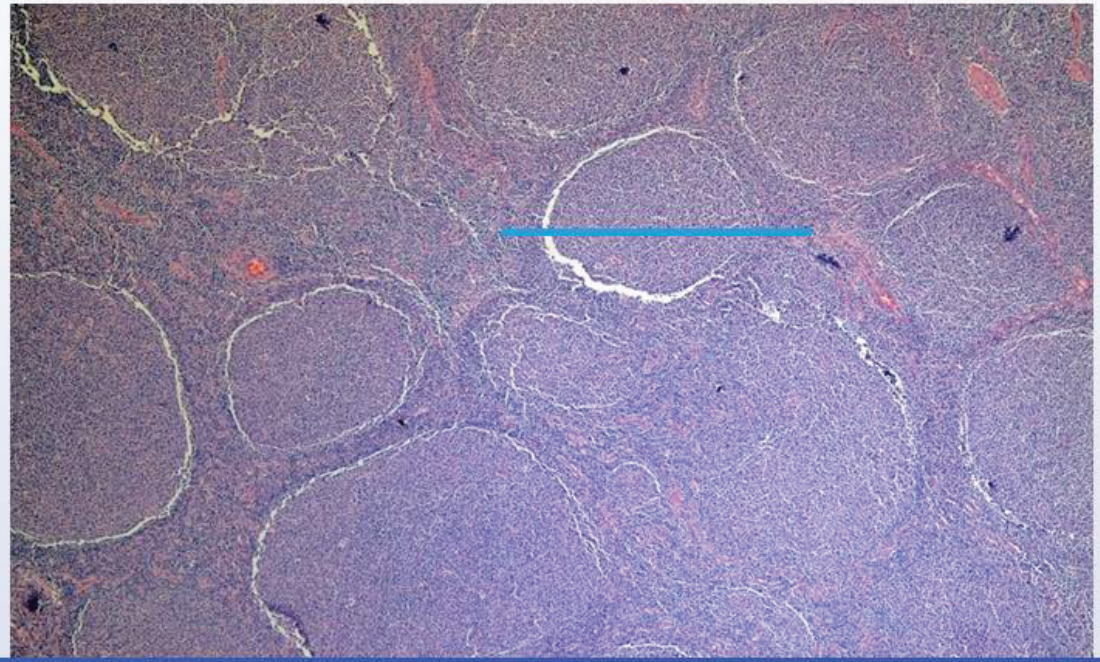


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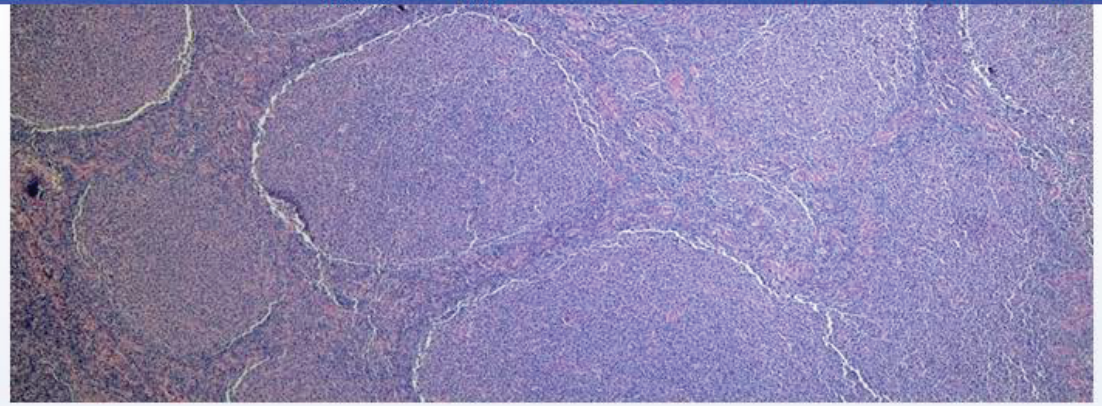
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A 35-year-old man is being evaluated for nontender cervical lymphadenopathy that he first noticed while shaving. A biopsy is performed, and a low-magnification image of the lymph node histology is shown below.



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Cytogenetic analysis would most likely demonstrate which of the following patterns?

A. BCL-2 overexpression

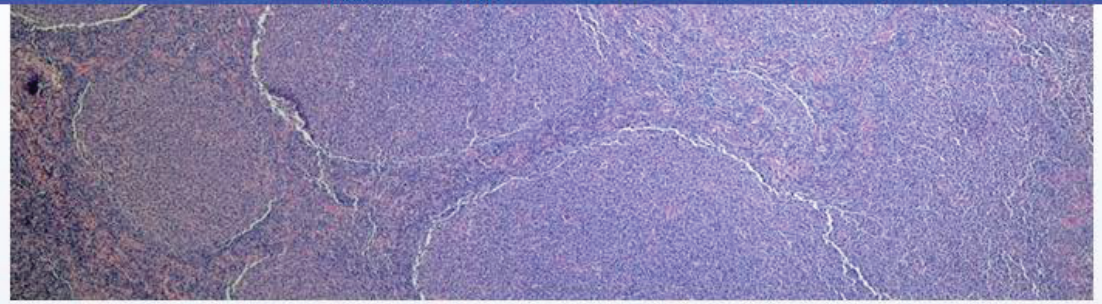
B. *BCR-ABL* rearrangement

C. C-MYC overexpression

D. Constitutive tyrosine kinase activation

E. N-MYC overexpression

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Cytogenetic analysis would most likely demonstrate which of the following patterns?

- A. BCL-2 overexpression (69%)
- B. ~~*BCR-ABL* rearrangement~~ (8%)
- C. ~~C-MYC overexpression~~ (16%)
- D. ~~Constitutive tyrosine kinase activation~~ (3%)
- E. ~~N-MYC overexpression~~ (2%)

Correct

69%

25 secs

10/23/2020

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The image demonstrates the classic histology of follicular lymphoma, a type of non-Hodgkin's lymphoma. Follicular lymphoma is a B-cell tumor composed predominantly of centrocytes (small cleaved cells) and fewer numbers of centroblasts (large noncleaved cells). At low magnification, aggregates of packed follicles (arrows) that obscure the normal lymph node architecture are seen. The t(14;18) translocation is found in 80%-90% of follicular lymphomas. The result is overexpression of the antiapoptotic gene product, BCL-2, and tumor formation.

(Choices B and D) *BCR-ABL* rearrangement t(9;22) is found in chronic myelogenous leukemia (CML). CML is a myeloproliferative disorder, not a lymphoproliferative disorder as shown in the image above. The *BCR-ABL* fusion gene directs the synthesis of a constitutively active protein tyrosine kinase that affects multiple intracellular signaling pathways, leading to uncontrolled proliferation.

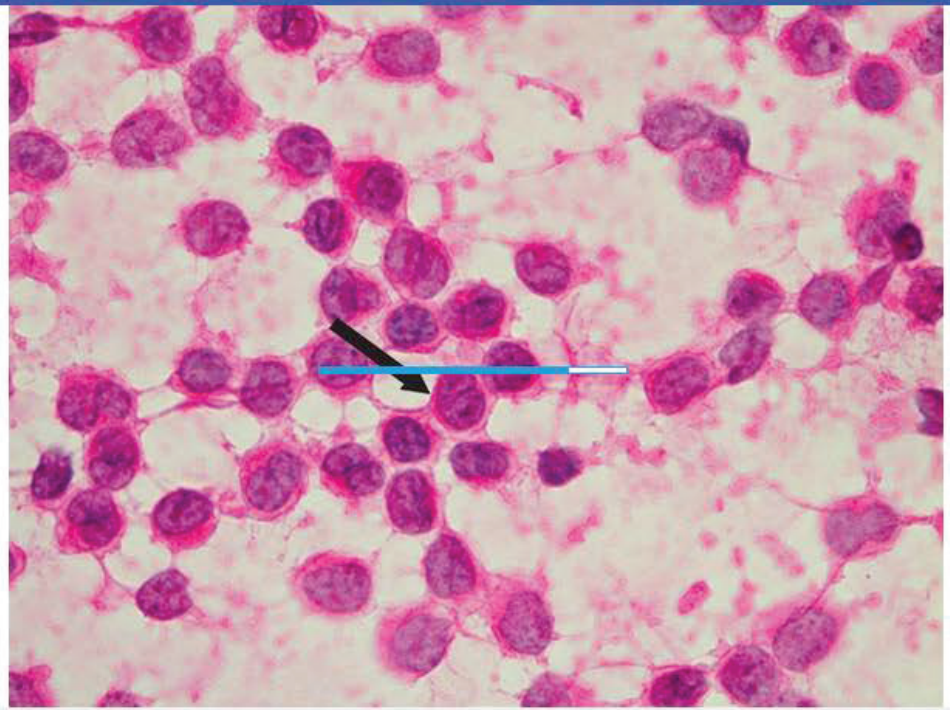
(Choice C) All Burkitt lymphomas are associated with translocations of the *C-MYC* gene on chromosome 8, usually onto the Ig heavy chain region of chromosome 14 [t(8;14)]. Histologically, Burkitt lymphoma shows a diffuse population of medium-sized lymphocytes with a "starry sky" appearance due to the high proliferation index and high rate of apoptosis.

(Choice E) Overexpression of N-MYC proto-oncogene protein is common in neuroblastoma and small cell

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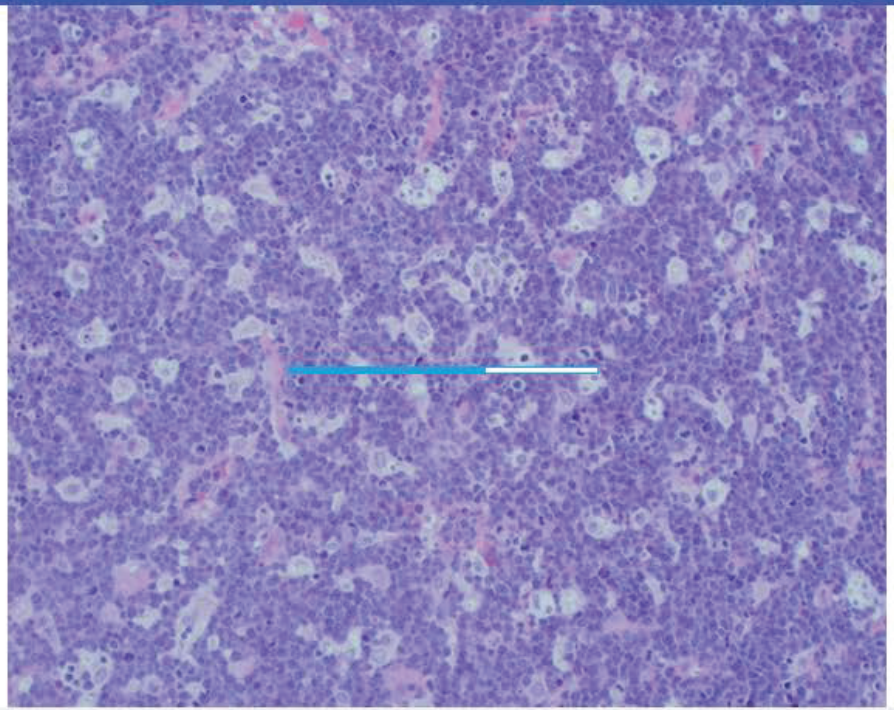


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CML is a myeloproliferative disorder, not a lymphoproliferative disorder as shown in the image above. The *BCR-ABL* fusion gene directs the synthesis of a constitutively active protein tyrosine kinase that affects multiple intracellular signaling pathways, leading to uncontrolled proliferation.

(Choice C) All Burkitt lymphomas are associated with translocations of the *C-MYC* gene on chromosome 8, usually onto the Ig heavy chain region of chromosome 14 [t(8;14)]. Histologically, Burkitt lymphoma shows a diffuse population of medium-sized lymphocytes with a "starry sky" appearance due to the high proliferation index and high rate of apoptosis.

(Choice E) Overexpression of N-MYC proto-oncogene protein is common in neuroblastoma and small cell carcinoma of the lung.

Educational objective:
Follicular lymphoma is characterized by aggregates of packed follicles that obscure the normal lymph node architecture. Ninety percent of patients with follicular lymphoma have the t(14;18) translocation, which causes overexpression of the antiapoptotic BCL-2 protein.

Pathology	Hematology & Oncology	Nonhodgkin lymphoma
Subject	System	Topic

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An 8-year-old boy comes to the office due to a mass in the right mandible. His family first noticed it a few months ago, and it has grown rapidly. He has had no fevers, chills, cough, or weight loss. The patient and his family recently immigrated to the United States from East Africa. He has no known medical problems. Temperature is 37 C (98.6 F). Physical examination shows a large tumor on the right mandible with palpable regional lymphadenopathy. A biopsy of the lesion is performed. Histopathologic examination shows a diffuse infiltrate of lymphoid cells with numerous mitotic figures; interspersed macrophages with clear cytoplasm are also seen. These lymphoid cells most likely have a chromosomal translocation that directly alters which of the following processes?

A. Apoptosis inhibition
B. DNA repair
C. Regulation of G1 to S-phase transition
D. Transcription activation
E. Tyrosine kinase upregulation

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months ago, and it has grown rapidly. He has had no fevers, chills, cough, or weight loss. The patient and his family recently immigrated to the United States from East Africa. He has no known medical problems. Temperature is 37 C (98.6 F). Physical examination shows a large tumor on the right mandible with palpable regional lymphadenopathy. A biopsy of the lesion is performed. Histopathologic examination shows a diffuse infiltrate of lymphoid cells with numerous mitotic figures; interspersed macrophages with clear cytoplasm are also seen. These lymphoid cells most likely have a chromosomal translocation that directly alters which of the following processes?

- A. Apoptosis inhibition (19%)
- B. DNA repair (2%)
- C. Regulation of G1 to S-phase transition (17%)
- ✓ D. Transcription activation (48%)
- E. Tyrosine kinase upregulation (12%)

Correct

48%

01 min, 04 secs

11/11/2020

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This patient likely has the endemic African form of **Burkitt lymphoma**, which primarily affects children and typically presents as a maxillary or mandibular mass. This type of lymphoma is strongly associated with **Epstein-Barr virus** (EBV) infection.

On histopathologic examination, Burkitt lymphoma consists of monomorphic, intermediate-sized lymphoid cells with round nuclei, multiple nucleoli, and basophilic cytoplasm. A high mitotic index and high cell death rate are typically seen. Benign macrophages that phagocytize the resulting cellular debris ("**tingible body macrophages**") are distributed throughout the malignant tissue. The clear cytoplasm of the macrophages contributes to the characteristic "starry sky" appearance of Burkitt lymphoma.

Most Burkitt lymphomas demonstrate a translocation between the c-*Myc* oncogene on the long arm of chromosome 8 and the Ig heavy chain region on chromosome 14 [**t(8;14)**]; this results in **Myc overexpression** due to the highly active immunoglobulin promoter in B cells. The product of c-*Myc* is a nuclear phosphoprotein that functions as a **transcription activator**, stimulating cell growth and proliferation.

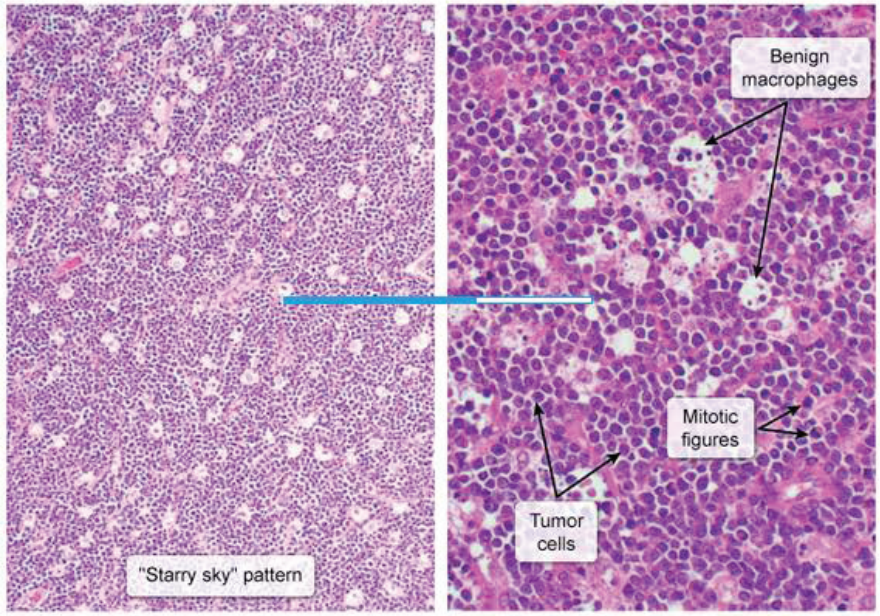
(Choice A) Follicular lymphoma is often characterized by a translocation between the long arm of chromosome 18 near the *BCL2* gene and the Ig heavy chain gene on chromosome 14 [t(14;18)]. This translocation leads to overexpression of the apoptosis inhibitor protein Bcl-2.

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Exhibit Display

Burkitt lymphoma



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translocation leads to overexpression of the apoptosis inhibitor protein Bcl-2.

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(Choice A) Follicular lymphoma is often characterized by a translocation between the long arm of chromosome 18 near the *BCL2* gene and the Ig heavy chain gene on chromosome 14 [t(14;18)]. This translocation leads to overexpression of the apoptosis inhibitor protein Bcl-2.

(Choice B) Mutations of DNA repair enzymes (eg, BRCA1, BRCA2) are associated with breast cancer, ovarian cancer, Lynch syndrome, xeroderma pigmentosum, Fanconi anemia, and many other diseases.

(Choice C) Translocation between the cyclin D1 locus on chromosome 11 and the Ig heavy chain locus on chromosome 14 [t(11;14)] is characteristic of mantle cell lymphoma. This abnormality results in increased production of cyclin D1, a promoter of G1 to S-phase transition during the cell cycle.

(Choice E) Translocation of the *ABL* gene from chromosome 9 to 22 [t(9;22)] results in the Philadelphia chromosome, a typical finding in chronic myeloid leukemia. *BCR-ABL*, the resulting fusion gene, encodes a protein with increased tyrosine kinase activity that inhibits apoptosis while promoting mitogenesis.

Educational objective:
Burkitt lymphoma is characterized by aggressive rapid growth and a "starry sky" microscopic appearance. Translocation between the c-*Myc* oncogene on the long arm of chromosome 8 with the Ig heavy chain region on chromosome 14 leads to overexpression of Myc, a nuclear phosphoprotein that functions as a transcription activator.

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A 45-year-old man comes to the emergency department due to epigastric abdominal pain and fatigue. He has had similar episodes of pain in the past. Temperature is 37.1 C (98.8 F), blood pressure is 128/69 mm Hg, pulse is 92/min, and respirations are 16/min. Physical examination shows mild epigastric tenderness and hepatomegaly. There is no jaundice or lymphadenopathy. Laboratory results are as follows:

Complete blood count	
Hemoglobin	9.0 g/dL
Mean corpuscular volume (MCV)	115 µm^3
Platelets	130,000/mm^3
Leukocytes	5,500/mm^3

CT scan of the abdomen shows pancreatic calcifications. Right upper quadrant ultrasound reveals no evidence of gallstones. Which of the following processes is most likely responsible for this patient's anemia?

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Volume (MCV)

Platelets	130,000/mm^3
Leukocytes	5,500/mm^3

CT scan of the abdomen shows pancreatic calcifications. Right upper quadrant ultrasound reveals no evidence of gallstones. Which of the following processes is most likely responsible for this patient's anemia?

A. Diminished thymidine synthesis
B. Impaired globin chain synthesis
C. Impaired pyruvate decarboxylation
D. Low rate of intracellular transamination reactions
E. Reduced iron availability for hemoglobin synthesis

Submit

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Volume (MCV)

Platelets	130,000/mm^3
Leukocytes	5,500/mm^3

CT scan of the abdomen shows pancreatic calcifications. Right upper quadrant ultrasound reveals no evidence of gallstones. Which of the following processes is most likely responsible for this patient's anemia?

- ✓ A. Diminished thymidine synthesis (62%)
- B. ~~Impaired globin chain synthesis~~ (7%)
- C. Impaired pyruvate decarboxylation (9%)
- D. Low rate of intracellular transamination reactions (12%)
- E. ~~Reduced iron availability for hemoglobin synthesis~~ (8%)

Correct

62%
Answered correctly

02 mins, 04 secs
Time Spent

11/06/2020
Last Updated

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This patient's recurrent abdominal pain and pancreatic calcifications suggest **chronic pancreatitis**, the most common cause of which is ethanol abuse. His **hepatomegaly** is likely due to alcohol-associated hepatic steatosis. The patient also has **macrocytic anemia** (low hemoglobin and elevated mean corpuscular volume [MCV] >100 μm^3), which in alcoholics often develops due to folic acid deficiency (within months) or vitamin B_{12} deficiency (within years).

Both deficiencies lead to **megaloblastosis**, the underlying biochemical feature of which is a defect in DNA synthesis. Folic acid is a single carbon donor required for synthesis of purine and pyrimidine (eg, thymidine) bases incorporated in DNA. RNA and protein synthesis may continue relatively unaltered, leading to a state of unbalanced cytoplasmic growth with impaired cell division. Pancreatic insufficiency is also associated with vitamin B_{12} deficiency as pancreatic enzymes normally cleave R factor from B_{12}, allowing B_{12} to bind to intrinsic factor and be absorbed.

(Choice B) The thalassemias are disorders presenting with reduced or absent globin chain production. Almost all thalassemia cases result in hypochromia and microcytosis (low MCV).

(Choice C) Oxidative decarboxylation of pyruvate by pyruvate dehydrogenase requires thiamine pyrophosphate (TPP), a derivative of thiamine (vitamin B_1). Alcoholics may be prone to thiamine deficiency and could therefore suffer from impaired pyruvate decarboxylation, but this does not cause macrocytic

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(Choice C) Oxidative decarboxylation of pyruvate by pyruvate dehydrogenase requires thiamine pyrophosphate (TPP), a derivative of thiamine (vitamin B_1). Alcoholics may be prone to thiamine deficiency and could therefore suffer from impaired pyruvate decarboxylation, but this does not cause macrocytic anemia.

(Choice D) Vitamin B_6 (pyridoxine) catalyzes the transaminase reactions by acting as a carrier of the amino group. B_6 deficiency can cause an anemia that is hypochromic, microcytic (low MCV), and sideroblastic.

(Choice E) Iron deficiency anemia is typically hypochromic and microcytic (low MCV <80 μm^3).

Educational objective:
The underlying biochemical feature of megaloblastosis is a defect in DNA synthesis. In chronic alcoholics, megaloblastic macrocytic anemia can result from a nutritional deficiency of vitamin B_{12} or of folate, which impairs synthesis of purine and pyrimidine bases.

Pathology	Hematology & Oncology	Anemia
Subject	System	Topic

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A 67-year-old man comes to the office due to severe fatigue for the past several months. The patient cannot eat as much as he used to and has lost nearly 10 kg (22 lb) in the past 6 months. Physical examination shows mucosal pallor, hepatomegaly, and massive splenomegaly. Further evaluation reveals a gain-of-function mutation of a non-receptor tyrosine kinase protein in hematopoietic cells, leading to persistent activation of signal transducers and activators of transcription (STAT) proteins. This patient is most likely suffering from which of the following disorders?

A. Acute promyelocytic leukemia
B. Chronic lymphocytic leukemia
C. High-grade non-Hodgkin lymphoma
D. Mantle cell lymphoma
E. Primary myelofibrosis

Submit

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A 67-year-old man comes to the office due to severe fatigue for the past several months. The patient cannot eat as much as he used to and has lost nearly 10 kg (22 lb) in the past 6 months. Physical examination shows mucosal pallor, hepatomegaly, and massive splenomegaly. Further evaluation reveals a gain-of-function mutation of a non-receptor tyrosine kinase protein in hematopoietic cells, leading to persistent activation of signal transducers and activators of transcription (STAT) proteins. This patient is most likely suffering from which of the following disorders?

A. ~~Acute promyelocytic leukemia~~ (16%)
B. Chronic lymphocytic leukemia (27%)
C. High-grade non-Hodgkin lymphoma (8%)
D. ~~Mantle cell lymphoma~~ (8%)
✓ E. Primary myelofibrosis (39%)

Correct

39%
Answered correctly

02 mins, 07 secs
Time Spent

02/01/2021
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Chronic myeloproliferative disorders		
Disorder	**Diagnostic features**	**Mutation**
Chronic myelogenous leukemia	Constitutional symptoms (eg, fatigue, weight loss, excessive sweating), splenomegaly & **leukocytosis with marked left shift** (eg, myelocytes, metamyelocytes, band forms)	Philadelphia chromosome t(9:22) BCR-ABL fusion protein
Essential thrombocytosis	Hemorrhagic & thrombotic symptoms (eg, easy bruising, microangiopathic occlusion), **thrombocytosis** & megakaryocytic hyperplasia	JAK2
Polycythemia vera	Pruritus, erythromelalgia, splenomegaly, thrombotic complications, **erythrocytosis** & thrombocytosis	
Primary myelofibrosis	Severe fatigue, splenomegaly (often causing early satiety/abdominal discomfort), hepatomegaly, anemia & **bone marrow fibrosis**	

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The chronic myeloproliferative disorders are bone marrow diseases characterized by overproduction of

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The chronic myeloproliferative disorders are bone marrow diseases characterized by overproduction of myeloid cells. **Primary myelofibrosis** is caused by atypical megakaryocytic hyperplasia, which stimulates fibroblast proliferation, resulting in progressive replacement of the marrow space by extensive collagen deposition. In the early stages, there is marrow hypercellularity with minimal fibrosis, but as the disease progresses, **pancytopenia** can result. **Hepatomegaly** and massive **splenomegaly** develop because the loss of bone marrow hematopoiesis is compensated for by extramedullary hematopoiesis. The peripheral smear characteristically shows **teardrop**-shaped red blood cells (dacrocytes) and nucleated red blood cells.

With the exception of chronic myelogenous leukemia, the chronic myeloproliferative disorders (especially polycythemia vera) frequently harbor a mutation in the nonreceptor cytoplasmic tyrosine kinase, Janus kinase 2 (JAK2). This mutation results in **constitutive tyrosine phosphorylation activity**, and consequently, in the cytokine-independent activation of the signal transducers and activators of transcription **(STAT)** pathway. Once they are activated, STAT proteins translocate to the nucleus and promote transcription. A JAK2 inhibitor (ruxolitinib) has been approved for treatment of primary myelofibrosis.

(Choice A) In acute promyelocytic leukemia, t(15;17) leads to the formation of a fusion gene between the

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myelofibrosis.

(Choice A) In acute promyelocytic leukemia, t(15;17) leads to the formation of a fusion gene between the promyelocytic leukemia (*PML*) and the retinoic acid receptor alpha (*RARA*) genes. The abnormal PML/RARα fusion protein blocks differentiation of myeloid precursors.

(Choice B) Chronic lymphocytic leukemia is a lymphoproliferative disorder involving B lymphocytes. The most significant laboratory finding is marked lymphocytosis, with "smudge cells" seen on peripheral blood smear. The majority of cases exhibit increased expression of the proto-oncogene *BCL2*; a similar finding occurs in follicular lymphomas.

(Choices C and D) Several high-grade non-Hodgkin lymphomas (NHLs) are associated with cytogenetic abnormalities. The t(8;14) translocation involves the c-*Myc* oncogene and is common in Burkitt lymphoma, which is associated with Epstein-Barr virus infection and classically has a "starry sky" histological appearance. Mantle cell lymphoma is a low grade NHL characterized by t(11;14), leading to cyclin D1 overexpression.

Educational objective:
The chronic myeloproliferative disorders (polycythemia vera, essential thrombocytosis, and primary myelofibrosis) often have a mutation in Janus kinase 2 (JAK2), a cytoplasmic tyrosine kinase. This results

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most significant laboratory finding is marked lymphocytosis, with "smudge cells" seen on peripheral blood smear. The majority of cases exhibit increased expression of the proto-oncogene *BCL2*; a similar finding occurs in follicular lymphomas.

(Choices C and D) Several high-grade non-Hodgkin lymphomas (NHLs) are associated with cytogenetic abnormalities. The t(8;14) translocation involves the c-*Myc* oncogene and is common in Burkitt lymphoma, which is associated with Epstein-Barr virus infection and classically has a "starry sky" histological appearance. Mantle cell lymphoma is a low grade NHL characterized by t(11;14), leading to cyclin D1 overexpression.

Educational objective:

The chronic myeloproliferative disorders (polycythemia vera, essential thrombocytosis, and primary myelofibrosis) often have a mutation in Janus kinase 2 (JAK2), a cytoplasmic tyrosine kinase. This results in constitutive tyrosine kinase activity, and consequently, in the cytokine-independent activation of signal transducers and activators of transcription (STAT) proteins (JAK-STAT signaling pathway).

References

- Myeloproliferative disorders.

Pathology Hematology & Oncology Myelofibrosis

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A 6-year-old boy is brought to the office due to fatigue and abdominal distension. The parents state that the patient bruises easily and appears pale. Physical examination shows subconjunctival pallor and several ecchymoses on the boy's extremities. His abdomen is distended with nontender massive splenomegaly and moderate hepatomegaly. Laboratory studies reveal that his hemoglobin level is 8 g/dL, leukocyte count is 3,800 cells/mm^3, and platelet count is 90,000 cells/mm^3. Bone marrow aspirate results are shown in the exhibit. Which of the following is the most likely diagnosis?

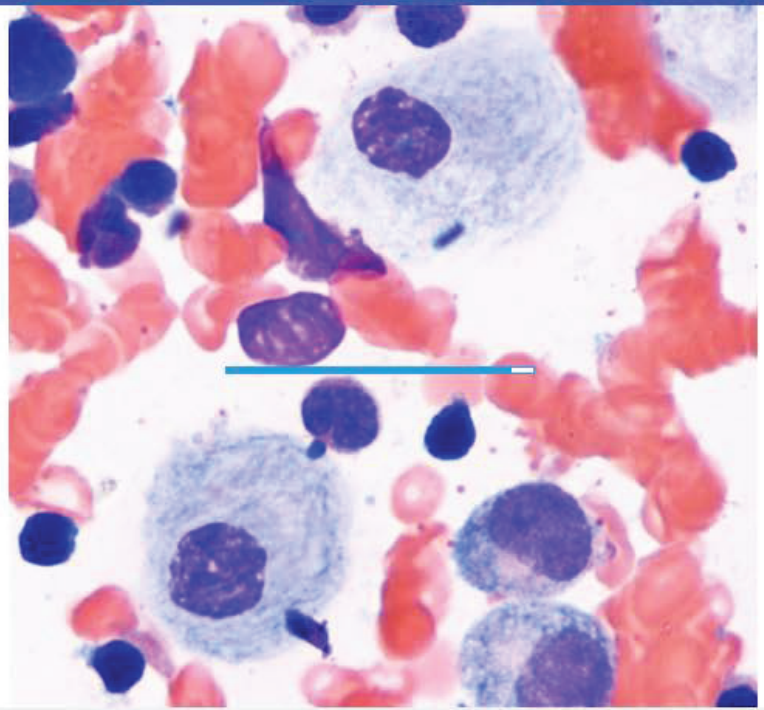
A. Acute lymphoblastic leukemia
B. Epstein-Barr virus
C. Fanconi anemia
D. Gaucher disease
E. Parvovirus B19

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A 6-year-old boy is brought to the office due to fatigue and abdominal distension. The parents state that the patient bruises easily and appears pale. Physical examination shows subconjunctival pallor and several ecchymoses on the boy's extremities. His abdomen is distended with nontender massive splenomegaly and moderate hepatomegaly. Laboratory studies reveal that his hemoglobin level is 8 g/dL, leukocyte count is 3,800 cells/mm^3, and platelet count is 90,000 cells/mm^3. Bone marrow aspirate results are shown in the exhibit. Which of the following is the most likely diagnosis?

A. Acute lymphoblastic leukemia (32%)
B. Epstein-Barr virus (4%)
C. Fanconi anemia (9%)
✓ D. Gaucher disease (40%)
E. Parvovirus B19 (12%)

Correct

40%
Answered correctly

01 min, 07 secs
Time Spent

09/01/2020
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Gaucher disease is an autosomal recessive lysosomal storage disease caused by a **deficiency of beta-glucocerebrosidase**. This enzyme is normally found in lysosomes where it functions to break down glucocerebroside (a glycolipid component of cell membranes). Deficiency leads to **accumulation of glucocerebroside** within the lysosomes of macrophages as they engulf and digest cellular debris; the resulting **lipid-laden macrophages** (Gaucher cells) have a characteristic "wrinkled tissue paper" appearance and can be found in the bone marrow and other affected tissues (eg, spleen).

Clinical manifestations develop as abnormal Gaucher cells accumulate within body tissues and secrete lysosomal proteases and cytokines that disrupt cellular function. The onset of symptoms varies from childhood to early adulthood and includes the following:

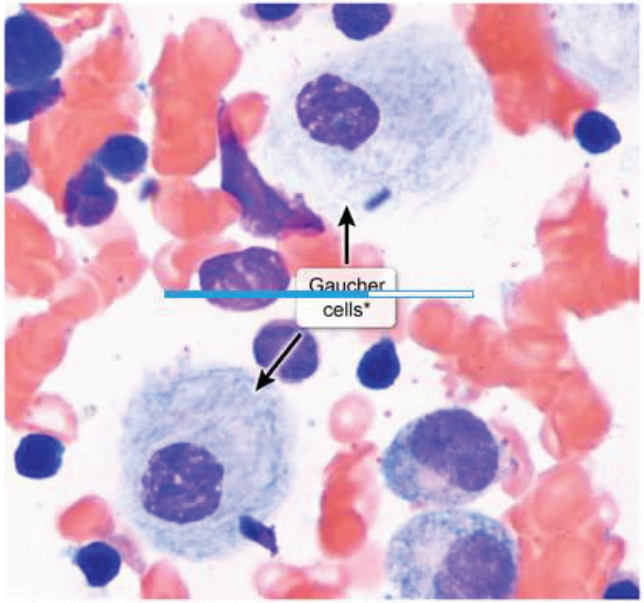
- Abdominal distension and **hepatosplenomegaly** due to accumulation of Gaucher cells in the liver and spleen
- **Bone pain** due to marrow invasion and release of inflammatory mediators, resulting in osteolytic lesions and bone infarction
- **Pancytopenia** due to splenic sequestration (enlarged spleen breaks down blood cells faster than they are produced) and bone marrow infiltration, resulting in easy bleeding and bruising, pallor and fatigue, and leukopenia

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Exhibit Display

Gaucher disease



*"Wrinkled tissue paper" cytoplasm due to glucocerebroside accumulation ©UWorld

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- **Pancytopenia** due to splenic sequestration (enlarged spleen breaks down blood cells faster than they are produced) and bone marrow infiltration, resulting in easy bleeding and bruising, pallor and fatigue, and leukopenia

(Choice A) Acute lymphoblastic leukemia is one of the most common childhood cancers. Although leukemia can present with pancytopenia and hepatosplenomegaly, bone marrow or peripheral blood smear would reveal lymphoblasts.

(Choice B) Epstein-Barr virus infection can present with fever, pharyngitis, cervical lymphadenopathy, fatigue, and splenomegaly. Atypical reactive lymphocytes would likely be found on peripheral blood smear, and Gaucher cells would not be expected in the bone marrow aspirate.

(Choice C) Fanconi anemia is an inherited cause of aplastic anemia. In addition to pancytopenia, patients often have hypo/hyperpigmented patches, short stature, and hypoplastic thumbs, as well as an increased risk of malignancy (eg, acute myeloid leukemia).

(Choice E) Parvovirus B19, a common cause of erythema infectiosum, can trigger a transient aplastic crisis in those with an underlying hematologic abnormality (eg, sickle cell disease, hereditary spherocytosis). Bone marrow aspirate would reveal erythroid precursors with intranuclear viral inclusions.

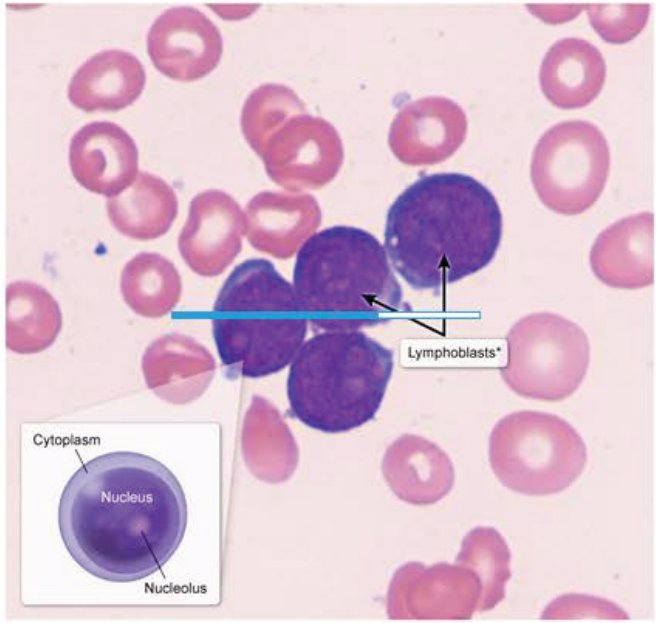
Educational objective:

https://t.me/USMLEWorldStep1

- **Pancytopenia** due to splenic sequestration (enlarged spleen breaks down blood cells faster than they

Exhibit Display

Acute lymphoblastic leukemia



*High nuclear-to-cytoplasmic ratio, immature chromatin, and visible nucleoli

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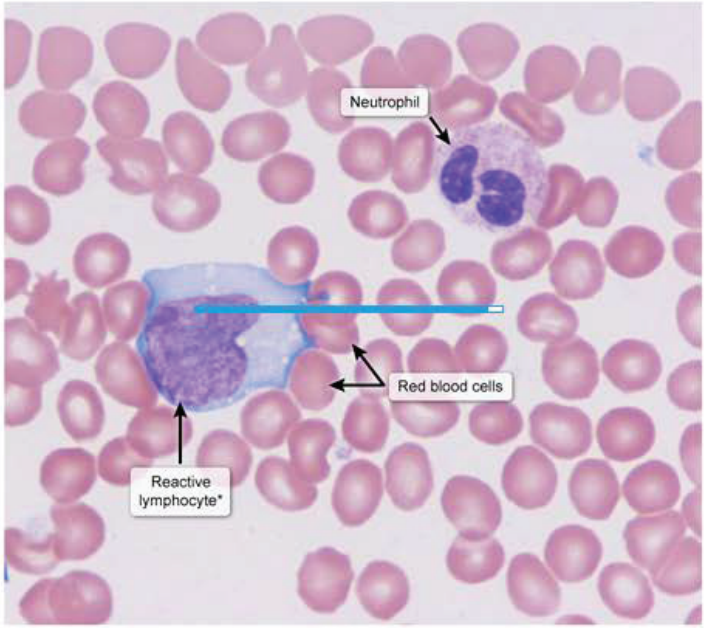
Educational objective:

https://t.me/USMLEWorldStep1

- **Pancytopenia** due to splenic sequestration (enlarged spleen breaks down blood cells faster than they

Exhibit Display

Epstein-Barr virus



*Large lymphocyte with abundant cytoplasm conforming to nearby red blood cells

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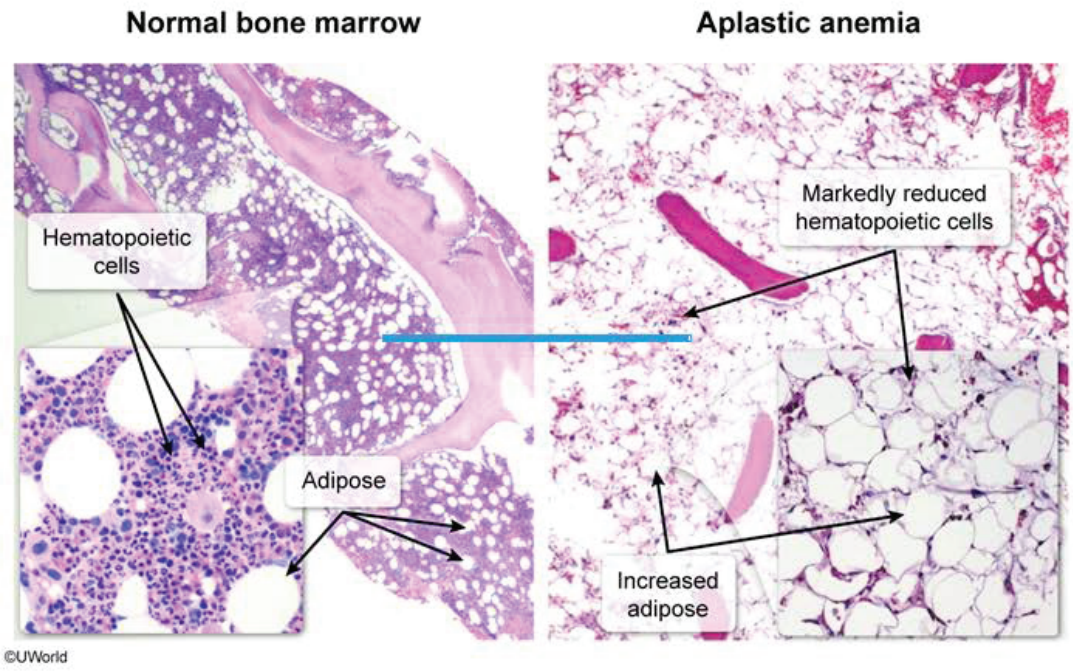
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Educational objective:

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- Pancytopenia due to splenic sequestration (enlarged spleen breaks down blood cells faster than they

Exhibit Display



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Educational objective:

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and Gaucher cells would not be expected in the bone marrow aspirate.

(Choice C) Fanconi anemia is an inherited cause of aplastic anemia. In addition to pancytopenia, patients often have hypo/hyperpigmented patches, short stature, and hypoplastic thumbs, as well as an increased risk of malignancy (eg, acute myeloid leukemia).

(Choice E) Parvovirus B19, a common cause of erythema infectiosum, can trigger a transient aplastic crisis in those with an underlying hematologic abnormality (eg, sickle cell disease, hereditary spherocytosis). Bone marrow aspirate would reveal erythroid precursors with intranuclear viral inclusions.

Educational objective:

Gaucher disease is a lysosomal storage disorder caused by beta-glucocerebrosidase deficiency that presents with bone pain, hepatosplenomegaly, and cytopenias. Glucocerebroside accumulation leads to distended macrophages with a "wrinkled tissue paper" appearance (Gaucher cells) that can be found in affected tissues (eg, bone marrow).

References

- Clinical manifestations and management of Gaucher disease.

Pathology Hematology & Oncology Gauchers Disease

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A 2-week-old girl is brought to her primary care provider for a routine visit. The patient was born by normal spontaneous vaginal delivery at 39 weeks gestation. The mother is breastfeeding exclusively, and the infant has regained her birth weight. Newborn screening results from hemoglobin electrophoresis are as follows:

Hemoglobin F	70%
Hemoglobin A	20%
Hemoglobin S	10%

The patient's mother has sickle cell trait, and a maternal cousin has sickle cell anemia. Examination shows a well-appearing infant with no pallor or splenomegaly. Which of the following is most likely true about this patient?

A. Life expectancy will be shorter than average

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	A	20%
	Hemoglobin S	10%

The patient's mother has sickle cell trait, and a maternal cousin has sickle cell anemia. Examination shows a well-appearing infant with no pallor or splenomegaly. Which of the following is most likely true about this patient?

A. Life expectancy will be shorter than average
B. Mean corpuscular volume will be decreased
C. Reticulocyte count will be elevated
D. She has relative protection from *Plasmodium falciparum*
E. She will likely develop pain crises

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A	20%
Hemoglobin S	10%

The patient's mother has sickle cell trait, and a maternal cousin has sickle cell anemia. Examination shows a well-appearing infant with no pallor or splenomegaly. Which of the following is most likely true about this patient?

A. Life expectancy will be shorter than average (1%)
B. Mean corpuscular volume will be decreased (2%)
C. Reticulocyte count will be elevated (5%)
D. She has relative protection from *Plasmodium falciparum* (85%)
E. She will likely develop pain crises (4%)

Correct
85%
01 min, 59 secs
09/20/2020

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Explanation

Sickle cell trait	
Clinical features	• Usually no symptoms of sickle cell anemia • More prevalent in African, Middle-Eastern & Mediterranean countries; African American & Hispanic individuals • No change in overall life expectancy
Diagnosis	• Normal hemoglobin, reticulocyte count, RBC indices & morphology • Hemoglobin electrophoresis shows both Hb A & Hb S, with the amount of Hb A greater than Hb S

Hb A = hemoglobin A; **Hb S** = hemoglobin S; **RBC** = red blood cells.

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This patient's hemoglobin electrophoresis from her newborn screen is most consistent with **sickle cell trait**. At birth, infants who are **heterozygous** for sickle cell trait typically have the greatest amount of fetal hemoglobin (Hb F), followed by hemoglobin A (Hb A), and the smallest amount of hemoglobin S (Hb S).

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This patient's hemoglobin electrophoresis from her newborn screen is most consistent with **sickle cell trait**. At birth, infants who are **heterozygous** for sickle cell trait typically have the greatest amount of fetal hemoglobin (Hb F), followed by hemoglobin A (Hb A), and the smallest amount of hemoglobin S (Hb S). Hb A continues to be higher than Hb S throughout the lifetime of these patients as Hb F naturally declines, offering protection from sickle cell anemia, aplastic crises, and splenic sequestration. Patients with sickle cell trait are usually **asymptomatic** with normal hemoglobin level, reticulocyte count, and red blood cell (RBC) indices. However, they may develop hematuria, priapism, and increased incidence of urinary tract infections. Splenic infarction at high altitudes has also been reported.

Patients with sickle cell trait have **relative protection from *Plasmodium falciparum* (malaria)**, resulting in lower rates of severe malaria and hospitalization than seen in the general population. Possible mechanisms include increased sickling of parasitized sickle cell trait RBCs and accelerated removal of these cells by the splenic monocyte-macrophage system. These patients are not immune to malaria, however, and those visiting malaria-endemic areas should still receive prophylaxis.

(Choice A) Life expectancy of patients with sickle cell trait is no different than that of the general population. Patients who are homozygous for the sickle cell mutation have a decreased life expectancy due to significant complications of disease (eg, acute chest syndrome, infection from encapsulated organisms).

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This patient's hemoglobin electrophoresis from her newborn screen is most consistent with **sickle cell**

Exhibit Display

Hemoglobin electrophoresis patterns

Diagnosis	Hemoglobin A	Hemoglobin S	Hemoglobin F
Normal	~99%	0%	<1%
Sickle cell disease	0%	85-95%	5-15%
Sickle cell trait	50-60%	35-45%	<2%

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organisms).

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however, and those visiting malaria-endemic areas should still receive prophylaxis.

(Choice A) Life expectancy of patients with sickle cell trait is no different than that of the general population. Patients who are homozygous for the sickle cell mutation have a decreased life expectancy due to significant complications of disease (eg, acute chest syndrome, infection from encapsulated organisms).

(Choices B and C) Patients with sickle cell trait typically have normal RBC indices and reticulocyte counts. Individuals with sickle cell anemia (eg, no normal Hb A) will have an elevated reticulocyte count but will maintain a normal mean corpuscular volume.

(Choice E) It is unlikely that this patient will develop painful crises as she is protected by the predominance of Hb A (normal hemoglobin) over Hb S. Vaso-occlusive pain crises that develop in patients with sickle cell anemia are thought to occur when Hb S polymerizes and causes the RBCs to assume a sickle shape, typically in response to a trigger (eg, cold weather, dehydration).

Educational objective:
Patients with sickle cell trait are typically asymptomatic and have relative protection from malaria caused by *Plasmodium falciparum*. These patients usually have normal hemoglobin, reticulocyte, and red blood cell index values. Life expectancy is the same as that of the general population.

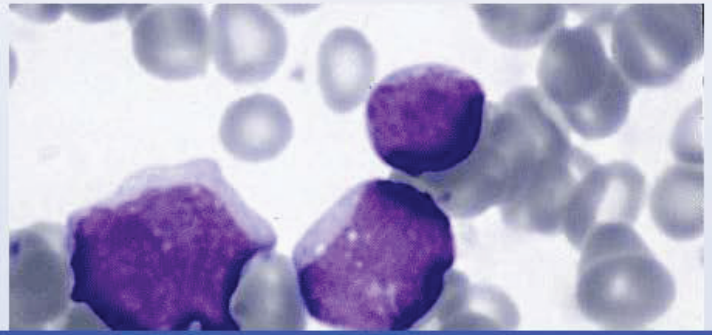
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A mother brings her 6-year-old son to his pediatrician because he has been having recurrent nosebleeds. Physical examination reveals diffuse petechiae. Laboratory studies show:

Complete blood count

Hemoglobin	9.0 g/L
Platelet count	20,000/mm^3
Leukocyte count	14,500/mm^3

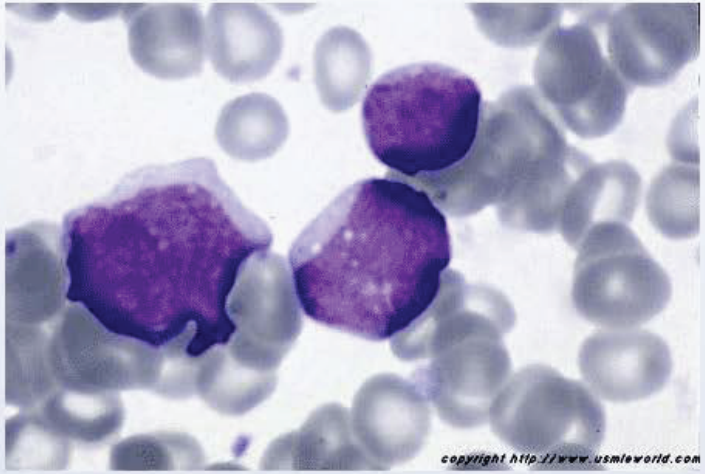
Bone marrow aspiration reveals the following:



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Platelet count	20,000/mm^3
Leukocyte count	14,500/mm^3

Bone marrow aspiration reveals the following:



The large cells at the center of the slide demonstrate positive immunostaining for terminal deoxynucleotidyltransferase (TdT). They express surface CD19 and CD10 as well. What is the most likely diagnosis?

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The large cells at the center of the slide demonstrate positive immunostaining for terminal deoxynucleotidyltransferase (TdT). They express surface CD19 and CD10 as well. What is the most likely diagnosis?

A. Precursor B-cell leukemia
B. Precursor T-cell leukemia
C. Mature B-cell leukemia
D. Mature T-cell leukemia
E. Hodgkin's lymphoma

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The large cells at the center of the slide demonstrate positive immunostaining for terminal deoxynucleotidyltransferase (TdT). They express surface CD19 and CD10 as well. What is the most likely diagnosis?

- A. Precursor B-cell leukemia (76%)
- B. Precursor T-cell leukemia (9%)
- C. Mature B-cell leukemia (9%)
- D. Mature T-cell leukemia (2%)
- E. Hodgkin's lymphoma (2%)

Correct

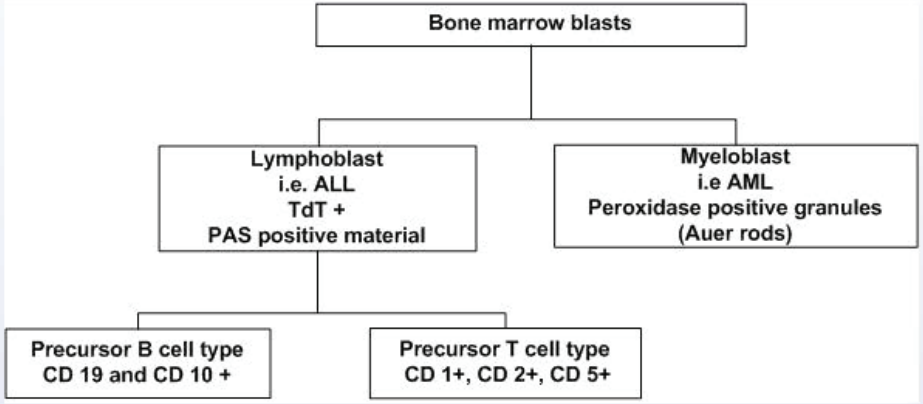
76%
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Explanation



This bone marrow smear shows several lymphoblasts with a high nuclear-to-cytoplasmic ratio, variably condensed nuclear chromatin, and prominent nucleoli. The presence of these immature cells excludes choices C, D & E. The differential diagnosis of this acute lymphoblastic leukemia (ALL) includes precursor B-cell leukemia (precursor B-ALL) and precursor T-cell leukemia (precursor T-ALL). Precursor B-ALL and precursor T-ALL can be distinguished from each other *only* by immunophenotyping. Lymphoblasts in precursor B-ALL are positive for TdT, CD10, and almost always for CD19. In contrast, lymphoblasts in

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CD 19 and CD 10 +

CD 1+, CD 2+, CD 5+

This bone marrow smear shows several lymphoblasts with a high nuclear-to-cytoplasmic ratio, variably condensed nuclear chromatin, and prominent nucleoli. The presence of these immature cells excludes choices C, D & E. The differential diagnosis of this acute lymphoblastic leukemia (ALL) includes precursor B-cell leukemia (precursor B-ALL) and precursor T-cell leukemia (precursor T-ALL). Precursor B-ALL and precursor T-ALL can be distinguished from each other *only* by immunophenotyping. Lymphoblasts in precursor B-ALL are positive for TdT, CD10, and almost always for CD19. In contrast, lymphoblasts in precursor T-ALL are TdT positive and variably express CD1a and the T-cell markers CD2, CD3, CD4, CD5, CD7, and CD8.

ALL is primarily a disease of children (75% occurs in children under six years of age). Most patients with precursor B-ALL present with evidence of bone marrow failure: thrombocytopenia and/or anemia and/or neutropenia. The leukocyte count may be normal, decreased or increased.

(Choice B) Precursor T-ALL accounts for about 15% of all childhood ALL and is more common in adolescents than younger children. Patients typically present with a high leukocyte count and often a large mediastinal mass. The lymphoblasts in precursor T-ALL variably express CD1a and T-cell markers like CD3, CD4, and CD8.

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(Choice C) Mature B-cell leukemia (or chronic lymphocytic leukemia/small lymphocytic lymphoma, CLL/SLL) is a neoplasm of small, round, monomorphic B-lymphocytes in the peripheral blood, bone marrow and lymph nodes. These neoplastic lymphocytes express CD19 (B-cell marker) and coexpress CD5 (T-cell marker) on their surface.

(Choice D) Mature T-cell leukemia is a group of uncommon neoplasms that are derived from mature or post-thymic T-cells. Findings would include more mature lymphocytes (not blasts) expressing T-cell markers.

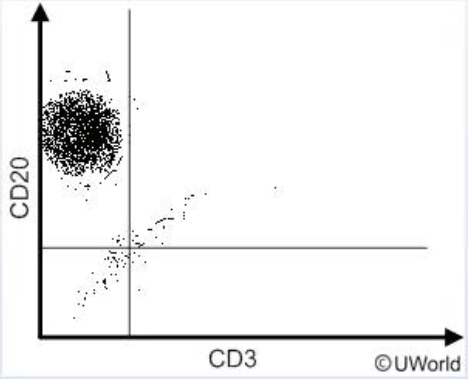
(Choice E) Hodgkin's lymphoma can involve the bone marrow, but blasts are not prominent. The classic bone marrow finding is Reed-Sternberg cells (large cells with abundant slightly basophilic cytoplasm and at least two nuclear lobes or nuclei).

Educational Objective:
Precursor B-ALL and precursor T-ALL can only be distinguished by immunophenotyping. The lymphoblasts in precursor B-ALL are TdT+, CD10+ and CD19+, whereas the lymphoblasts in precursor T-ALL express T-cell markers (e.g. CD2, CD3, CD4, CD5, CD7 and CD8), TdT and CD1a.

Pathology Hematology & Oncology Acute lymphoblastic leukemia

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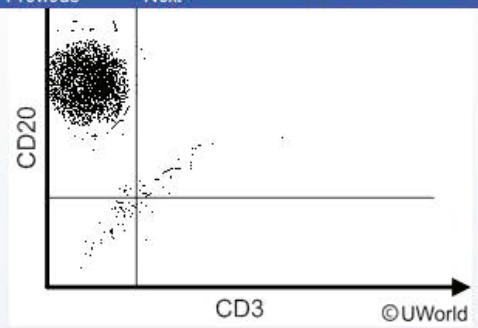
A 67-year-old woman is evaluated for worsening fatigue and exertional dyspnea. She has no prior medical conditions and takes no medications. The patient does not use tobacco, alcohol, or illicit drugs and consumes a balanced diet. Vital signs are within normal limits. Physical examination is notable for mucosal pallor. Stool testing for occult blood is negative. Laboratory studies reveal that hemoglobin is 6.7 g/dL, white blood cell count is 35,000/mm^3, and platelets are 45,000/mm^3. Peripheral blood flow cytometry of the white blood cell population is shown below.



Which of the following is the most likely diagnosis?

A. Adult T-cell leukemia

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Which of the following is the most likely diagnosis?

A. Adult T-cell leukemia

B. Aplastic anemia

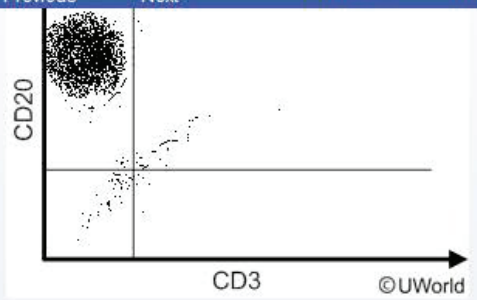
C. Chronic lymphocytic leukemia

D. Chronic myeloid leukemia

E. Classic Hodgkin lymphoma

Submit

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Which of the following is the most likely diagnosis?

A. ~~Adult T-cell leukemia~~ (3%)

B. ~~Aplastic anemia~~ (1%)

C. Chronic lymphocytic leukemia (72%)

D. ~~Chronic myeloid leukemia~~ (8%)

E. Classic Hodgkin lymphoma (13%)

Correct

72%

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02/03/2021

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This patient's symptomatic anemia (eg, fatigue, weakness), thrombocytopenia, and leukocytosis are associated with a predominance of CD20-positive cells (a B-cell surface marker), raising strong suspicion for **chronic lymphocytic leukemia** (CLL). In CLL, **mature B cells** progressively accumulate in the bone marrow and peripheral blood due to oncogenic mutations that **inhibit apoptosis**. Although most patients are asymptomatic for years, accumulation of B cells in the bone marrow eventually chokes out normal hematopoiesis, leading to symptomatic **anemia**, **thrombocytopenia**, and infections (due to neutropenia).

Patients with CLL usually have dramatic elevations in peripheral leukocyte count (often >100,000/mm^3) and characteristic findings on peripheral blood smear (eg, numerous small lymphocytes, smudge cells). The diagnosis is supported by flow cytometry of peripheral blood revealing a **clonal population** of leukocytes with expression of B-cell surface markers such as **CD19**, **CD20**, and **CD23**.

(Choice A) T-cell leukemia is marked by the clonal expansion of a leukocyte population with T-cell surface markers such as CD2, CD3, and CD4. However, this patient's flow cytometry shows very few CD3-positive cells.

(Choice B) Aplastic anemia is characterized by bone marrow failure and is usually triggered by an infection, medication, radiation, toxic substance, or autoimmune disease. Patients have pancytopenia (not leukocytosis) and bone marrow biopsy shows a hypocellular marrow with morphologically normal

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leukocytosis) and bone marrow biopsy shows a hypocellular marrow with morphologically normal hematopoietic cells; a clonal population of B cells would not be seen.

(Choice D) Chronic myeloid leukemia is a myeloproliferative neoplasm characterized by peripheral leukocytosis due to numerous circulating granulocytes (eg, neutrophils in different stages of maturation). Diagnosis is generally made when cytogenetic studies reveal the *BCR-ABL* fusion gene. A predominant population of CD20-positive cells (B cells) would not be seen.

(Choice E) Classic Hodgkin lymphoma usually causes localized peripheral lymphadenopathy and B-symptoms (eg, fever, night sweats). The diagnosis is made by lymph node excision, which usually reveals Reed-Sternberg cells that are characteristically positive for CD15 and CD30 immunohistochemical stains. Anemia, thrombocytopenia, and leukocytosis would be atypical.

Educational objective:
Chronic lymphocytic leukemia is a lymphoproliferative disorder marked by the progressive accumulation of mature B cells. Most patients are asymptomatic for years but eventually develop anemia, thrombocytopenia, and/or neutropenia. The diagnosis is generally made when complete blood count reveals dramatic leukocytosis, and flow cytometry subsequently shows a clonal population of leukocytes with B-cell markers such as CD19, CD20, and CD23.

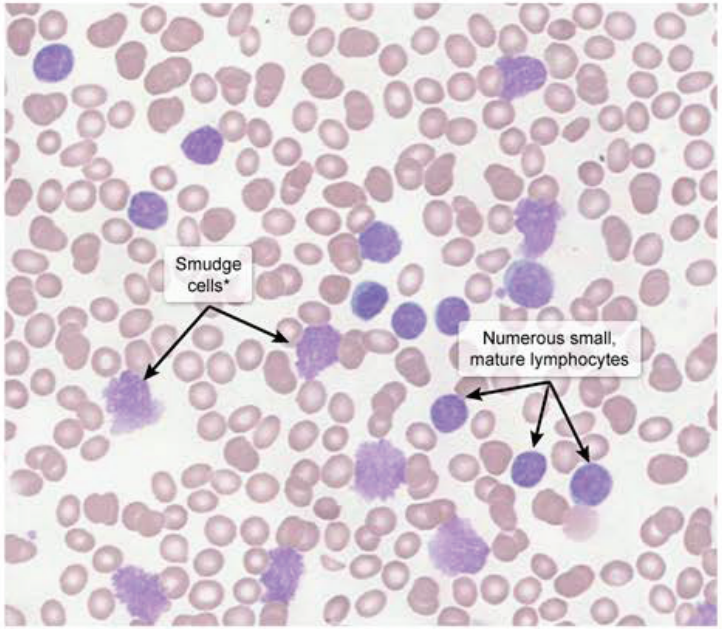
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72%
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02/03/2021

Exhibit Display

Chronic lymphocytic leukemia



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A 26-year-old woman, gravida 2 para 1, at 8 weeks gestation comes to the office due to pain and swelling of her left leg for the past day. The patient had a pulmonary embolism during her previous pregnancy, and prophylactic low-molecular-weight heparin therapy was initiated 6 days ago. She has no other medical conditions and takes prenatal vitamins. Physical examination shows left lower extremity edema and calf tenderness but no other abnormalities. Venous duplex ultrasonography reveals acute left femoral vein thrombosis. Platelet count, which was normal prior to anticoagulant therapy initiation, is 84,000/mm^3. Other blood cell counts and renal and liver function studies are within normal limits. Which of the following most likely predisposed this patient to her current condition?

A. Acquired protein C deficiency
B. Anti-platelet factor 4/heparin antibodies
C. Anti-platelet glycoprotein IIb/IIIa antibodies
D. Cold-precipitable immunoglobulins
E. Decreased ADAMTS13 level

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A. ~~Acquired protein C deficiency~~ (12%)
✓ B. Anti-platelet factor 4/heparin antibodies (71%)
C. Anti-platelet glycoprotein IIb/IIIa antibodies (4%)
D. Cold-precipitable immunoglobulins (1%)
E. Decreased ADAMTS13 level (9%)

Correct

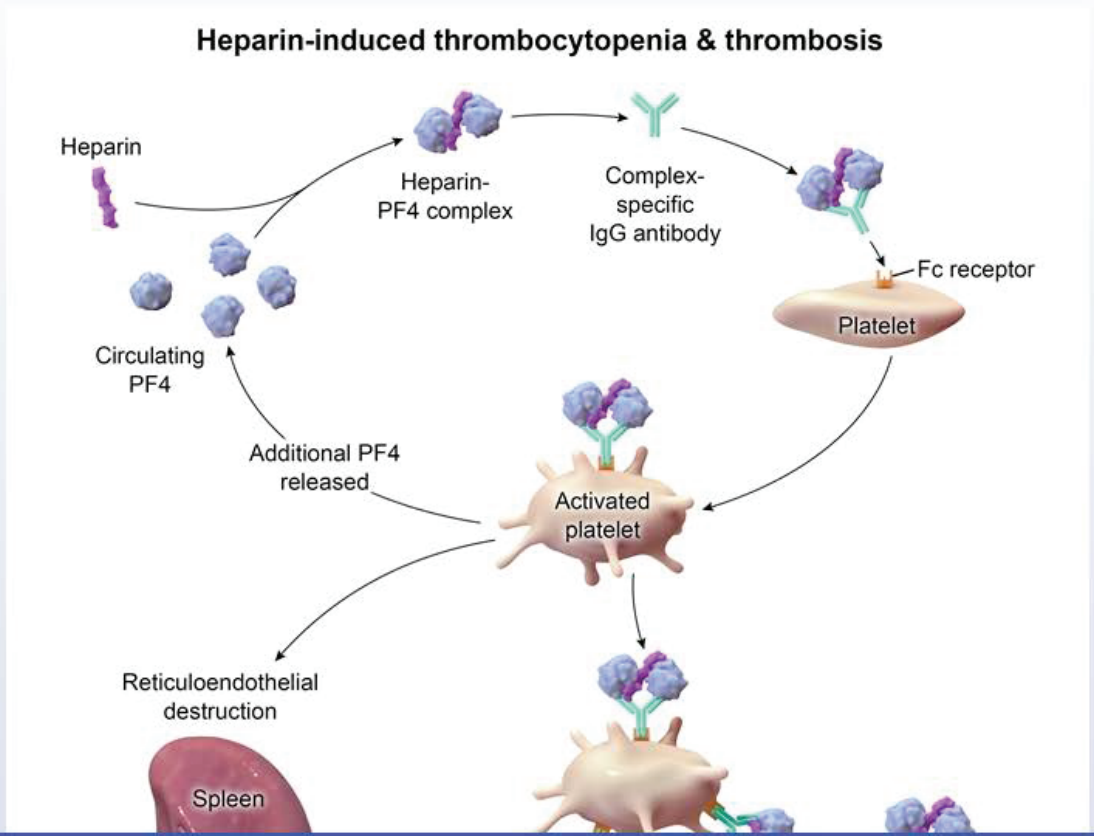
71%
Answered correctly

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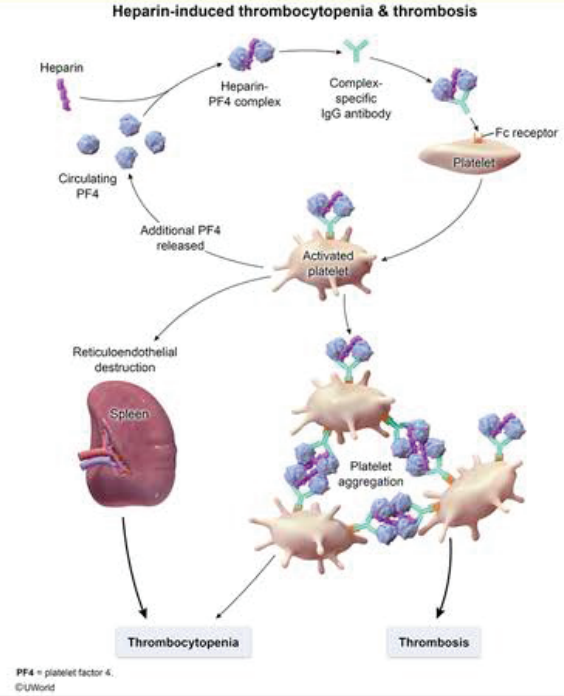
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This patient with a significant drop in platelet count and acute venous thromboembolism following recent exposure to low molecular weight heparin likely has **heparin-induced thrombocytopenia and thrombosis** (HITT), also known as heparin-induced thrombocytopenia type 2. HITT typically occurs 5-10 days following exposure to heparin products and is characterized by a large drop in platelet count. It is more common following exposure to unfractionated heparin but can occur following exposure to low-molecular weight heparin as well.

Platelet factor 4 (PF4) is a protein released from the alpha granules of platelets that plays a role in platelet aggregation. It also binds heparin and helps inactivate the molecule. The mechanism of HITT involves the generation of **IgG antibodies** to these complexes of heparin and PF4. The Fc component of the activated IgG antibodies then binds to additional platelets, resulting in further PF4 release and **widespread platelet activation**. This leads to a **prothrombotic state** that places patients at high risk for both arterial and venous thrombosis.

(Choice A) Acquired protein C deficiency occurs early in the course of warfarin therapy, as the inhibition of protein C by warfarin occurs more rapidly than the inhibition of other factors (ie, factors II, VII, IX, X). If not bridged with heparin when starting therapy, patients may develop warfarin-induced skin necrosis due to localized cutaneous thrombus formation.

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protein C by warfarin occurs more rapidly than the inhibition of other factors (ie, factors II, VII, IX, X). If not bridged with heparin when starting therapy, patients may develop warfarin-induced skin necrosis due to localized cutaneous thrombus formation.

(Choice C) Idiopathic thrombocytopenic purpura (ITP) results from splenic destruction of platelets labeled by IgG antibodies to glycoprotein IIb/IIIa receptors. ITP often causes very low platelet levels and is associated with bleeding complications rather than thrombosis.

(Choice D) Cryoglobulinemia can occur in the setting of autoimmune disease (eg, systemic lupus erythematosus) or viral infection (eg, hepatitis C) and causes systemic vasculitis characterized by fatigue, arthralgia, and purpuric rash. Marked thrombocytopenia is not typical.

(Choice E) Thrombotic thrombocytopenic purpura (TTP) results from decreased levels of the von Willebrand factor-cleaving protease ADAMTS13. The classic presentation of TTP is the pentad of fever, thrombocytopenia, microangiopathic hemolytic anemia, renal insufficiency, and neurologic dysfunction.

Educational objective:
Heparin-induced thrombocytopenia and thrombosis results from the production of IgG antibodies against complexes of heparin and platelet factor 4. The Fc component of these antibodies binds to platelets, resulting in widespread platelet activation and a prothrombotic state.

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A 12-year-old boy is evaluated due to fever, fatigue, and easy bruising. Physical examination shows pallor, generalized lymphadenopathy, and bone tenderness. Laboratory evaluation reveals anemia, thrombocytopenia, and leukocytosis with atypical lymphoblasts. Bone marrow biopsy is consistent with acute lymphoblastic leukemia. The patient is treated with combination chemotherapy, and 6-mercaptopurine is administered for maintenance of remission. Which of the following enzymes inactivates this drug?

A. Adenosine deaminase
B. Dihydrofolate reductase
C. Hypoxanthine-guanine phosphoribosyltransferase
D. Monoamine oxidase
E. P-450 mixed-function oxidase
F. Topoisomerase II
G. Xanthine oxidase

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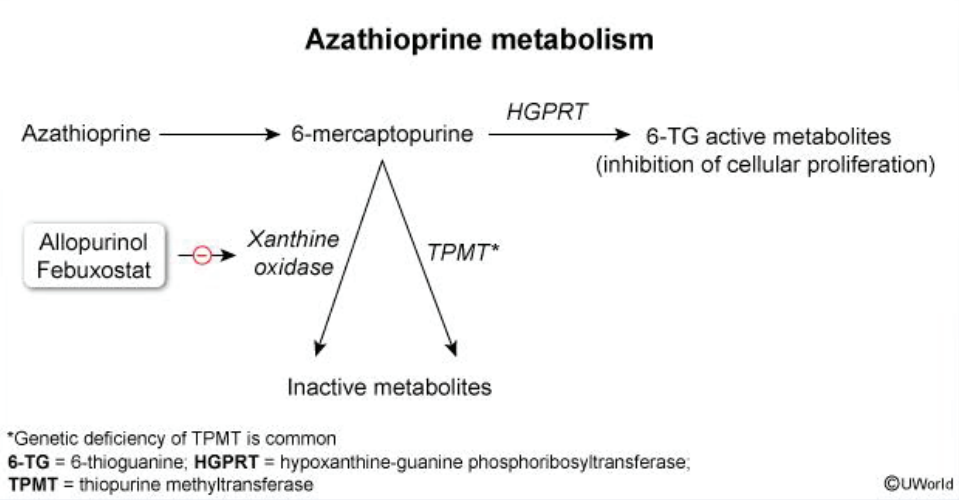
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generalized lymphadenopathy, and bone tenderness. Laboratory evaluation reveals anemia, thrombocytopenia, and leukocytosis with atypical lymphoblasts. Bone marrow biopsy is consistent with acute lymphoblastic leukemia. The patient is treated with combination chemotherapy, and 6-mercaptopurine is administered for maintenance of remission. Which of the following enzymes inactivates this drug?

A. Adenosine deaminase (6%)
B. Dihydrofolate reductase (4%)
C. Hypoxanthine-guanine phosphoribosyltransferase (13%)
D. Monoamine oxidase (1%)
E. P-450 mixed-function oxidase (4%)
F. Topoisomerase II (0%)
G. Xanthine oxidase (69%)

Correct
69%
01 min, 58 secs
10/18/2020

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6-mercaptopurine (6-MP) can be administered directly or in its prodrug form (ie, **azathioprine**). Following ingestion, 6-MP is converted by hypoxanthine-guanine phosphoribosyltransferase (HGPRT) into 6-thioguanine (6-TG) active metabolites **(Choice C)**. The 6-TG metabolites are purine analogues that act as false nucleotides to disrupt DNA and RNA synthesis and inhibit the proliferation of hematopoietic cells, a useful effect in the treatment of autoimmune disease, organ transplant rejection, and some types of cancer (eg, leukemia).

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(eg, leukemia).

6-MP is **metabolized into inactive metabolites** by 2 different enzymes, **xanthine oxidase** and **thiopurine methyltransferase** (TPMT), both of which are clinically important. Coadministration of 6-MP with a xanthine oxidase inhibitor (eg, allopurinol, febuxostat) slows the inactivation of 6-MP and shunts metabolism toward the production of 6-TG active metabolites; therefore, the dose of 6-MP must be significantly reduced. In addition, roughly 12% of the population has a genetic mutation resulting in low or absent activity of TPMT, creating a high risk of toxicity with the administration of 6-MP. Therefore, some clinicians recommend that patients undergo genetic testing for TPMT activity prior to initiating 6-MP (or azathioprine) therapy.

(Choice A) Adenosine deaminase (ADA) converts adenosine to inosine as part of purine metabolism. This enzyme is deficient in severe combined immunodeficiency but may be overexpressed in some malignancies. Cladribine, which is used in the treatment of hairy cell leukemia, is a cytotoxic purine analogue resistant to degradation by ADA.

(Choice B) Methotrexate is used in the treatment of cancer and rheumatologic disease. It inhibits dihydrofolate reductase, thereby blocking the conversion of dihydrofolate to tetrahydrofolate and disrupting the synthesis of thymidine and, to a lesser extent, purines.

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dihydrofolate reductase, thereby blocking the conversion of dihydrofolate to tetrahydrofolate and disrupting the synthesis of thymidine and, to a lesser extent, purines.

(Choice D) Monoamine oxidase inhibitors are used in the treatment of atypical depression; these agents inhibit degradation of the neurotransmitters norepinephrine, dopamine, and serotonin.

(Choice E) Cyclophosphamide, used to treat many types of cancer, requires bioactivation by the cytochrome P-450 mixed-function oxidase system.

(Choice F) Topoisomerase II is inhibited by the chemotherapeutic agents etoposide and teniposide.

Educational objective:
6-mercaptopurine (6-MP) is an immunosuppression drug that is inactivated by 2 enzymes, xanthine oxidase and thiopurine methyltransferase. Reduced function of either enzyme causes increased levels of the active metabolites of 6-MP, leading to increased immunosuppression and risk of toxicity.

References

- Implementation of TPMT testing.

Pharmacology	Hematology & Oncology	Chemotherapy
Subject	System	Topic

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A 24-year-old African-American man comes to the office after a rapid HIV test was positive at a health fair. Additional laboratory evaluation reveals a HIV viral load of 240,000 copies/mL and a CD4 count of 180 cells/mm^3. The patient is given a prescription for antiretroviral therapy. He is also given dapsone for *Pneumocystis jiroveci* pneumonia prophylaxis due to a history of rash with trimethoprim-sulfamethoxazole. Pneumococcal and influenza vaccines are administered. A few days later, the patient returns to the office due to fatigue, jaundice, and dark urine. Laboratory results now show the following:

Complete blood count

Hemoglobin	9.0 g/dL
Mean corpuscular volume	85 μm^3
Reticulocytes	7.1%
Platelets	234,000/mm^3
Leukocytes	5,500/mm^3

Coagulation studies are within normal limits. Peripheral smear reveals red blood cell fragments, microspherocytes, and bite cells. Which of the following is the most likely underlying cause of this patient's

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Mean corpuscular volume	85 μm^3
Reticulocytes	7.1%
Platelets	234,000/mm^3
Leukocytes	5,500/mm^3

Coagulation studies are within normal limits. Peripheral smear reveals red blood cell fragments, microspherocytes, and bite cells. Which of the following is the most likely underlying cause of this patient's symptoms?

A. Abnormal sickling due to medication
B. Disseminated intravascular coagulation
C. Enzyme-deficiency hemolytic anemia
D. Red blood cell cytoskeleton abnormality
E. Vaccine-induced hemolysis

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Reticulocytes	7.1%
Platelets	234,000/mm^3
Leukocytes	5,500/mm^3

Coagulation studies are within normal limits. Peripheral smear reveals red blood cell fragments, microspherocytes, and bite cells. Which of the following is the most likely underlying cause of this patient's symptoms?

A. Abnormal sickling due to medication (4%)
B. Disseminated intravascular coagulation (0%)
C. Enzyme-deficiency hemolytic anemia (88%)
D. Red blood cell cytoskeleton abnormality (3%)
E. Vaccine-induced hemolysis (2%)

Correct
88%
59 secs
12/06/2020

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Glucose-6-phosphate dehydrogenase deficiency	
Epidemiology	• Hemolytic anemia due to oxidative stress (infection, sulfa drugs, fava beans) • X-linked: Asian, African, or Middle Eastern descent
Manifestations	• Pallor & fatigue • Dark urine, jaundice & icterus • Abdominal/back pain
Laboratory findings	• Hemolysis: ↓ hemoglobin, ↓ haptoglobin, ↑ bilirubin & LDH, ↑ reticulocytes • Peripheral smear: bite cells & Heinz bodies • Negative Coombs test • ↓ G6PD activity level (may be normal during attack)
Management	• Remove or treat responsible agent/condition • Provide supportive care
G6PD = glucose-6-phosphate dehydrogenase; **LDH** = lactate dehydrogenase.	

This patient developed symptomatic anemia (eg, fatigue) and signs of hemolysis (eg, jaundice, dark urine)

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G6PD = glucose-6-phosphate dehydrogenase; **LDH** = lactate dehydrogenase.

This patient developed symptomatic anemia (eg, fatigue) and signs of hemolysis (eg, jaundice, dark urine) after taking dapsone for a few days, indicating likely glucose-6-phosphate dehydrogenase **(G6PD) deficiency**. G6PD catalyzes the first step of NADPH production. Because NADPH is required to generate the reduced form glutathione (a potent antioxidant), patients with G6PD deficiency lack sufficient reductive capacity to handle significant **oxidative stressors** and typically develop erythrocyte damage/lysis with acute infection, oxidative foods (eg, fava beans), and oxidative medications (eg, **dapsone**, primaquine).

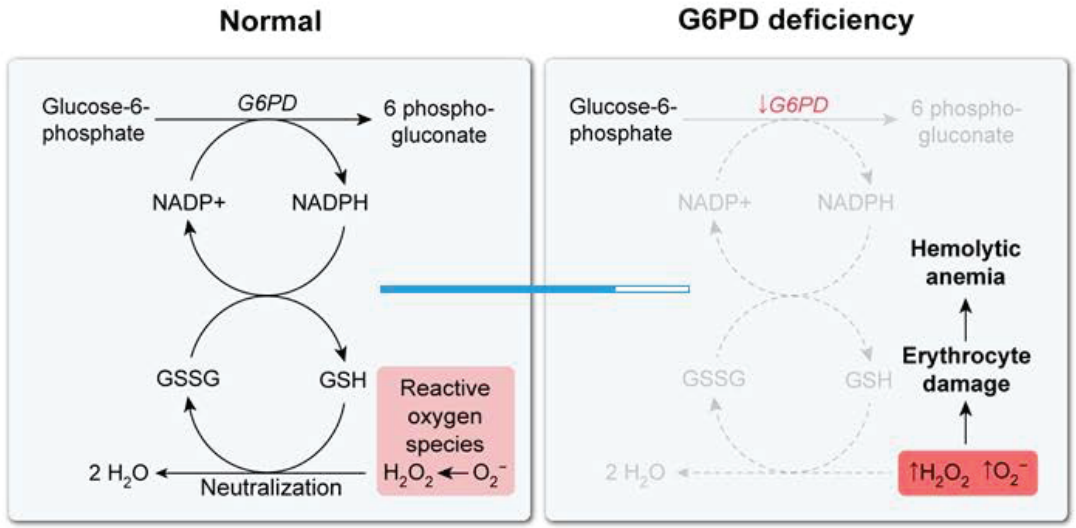
Oxidative injury to erythrocytes causes hemoglobin precipitation on the erythrocyte membrane (Heinz body) and impairs erythrocyte deformation while passing through the narrow sinusoids of the spleen. The damaged erythrocytes are identified and removed by splenic macrophages, leading to extravascular **hemolysis**.

Patients typically develop manifestations 2-4 days after the oxidative injury, including acute anemia and signs of elevated bilirubin (eg, **dark urine**, **jaundice**). Laboratory evaluation generally shows **significant reticulocytosis** because the bone marrow increases erythrocytosis to compensate for the anemia. Peripheral smear generally shows hemoglobin precipitation (Heinz bodies) on the periphery of red blood cells and bite cells due to phagocytic removal of precipitated hemoglobin by splenic macrophages.

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G6PD = glucose-6-phosphate dehydrogenase; **GSH** = glutathione; **GSSG** = glutathione disulfide.

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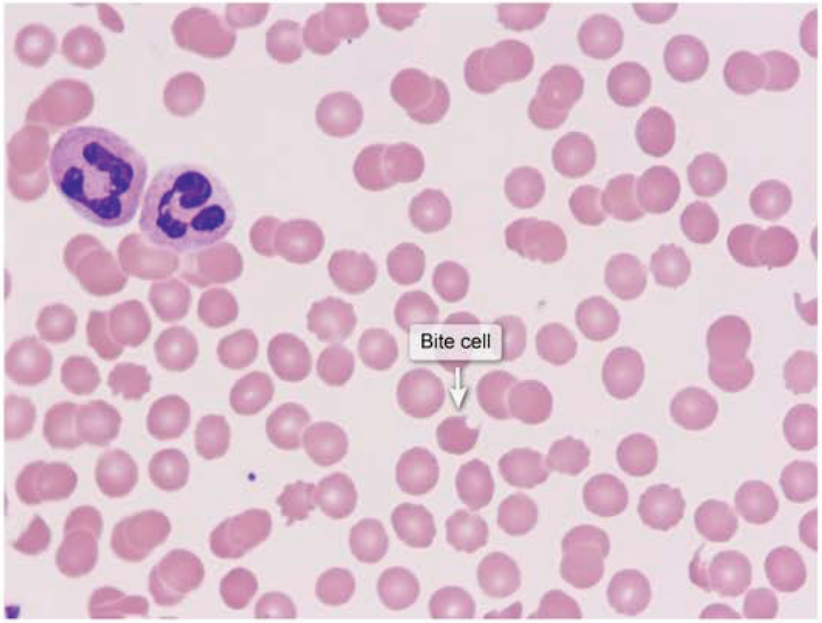
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G6PD deficiency anemia



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cells and bite cells due to phagocytic removal of precipitated hemoglobin by splenic macrophages. Because mild intravascular hemolysis also occurs (due to intravascular erythrocyte lysis from oxidative damage), schistocytes (fragmented red blood cells) and microspherocytes (round, dense schistocytes) are also frequently seen on peripheral smear.

(Choice A) Sickle cell anemia is a genetic mutation associated with erythrocyte sickling in the setting of deoxygenation and dehydration. Blood smear shows sickled red blood cells (not schistocytes), bite cells, and microspherocytes.

(Choice B) Disseminated intravascular coagulation is a consumptive coagulopathy characterized by intravascular clot formation, which shears red blood cells. Although schistocytes are seen on peripheral smear, Heinz bodies and bite cells are not. In addition, these patients have significant thrombocytopenia and prolonged coagulation times.

(Choice D) Hereditary spherocytosis, a genetic disorder marked by erythrocyte cytoskeleton abnormalities, is marked by abundant spherocytes, but not bite cells or schistocytes. In addition, this patient developed symptoms after dapsone administration, making G6PD more likely.

(Choice E) Pneumococcal and influenza vaccination does not typically trigger hemolysis. These vaccines can sometimes cause Guillain-Barré syndrome or rash.

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(Choice E) Pneumococcal and influenza vaccination does not typically trigger hemolysis. These vaccines can sometimes cause Guillain-Barré syndrome or rash.

Educational objective:
Glucose-6-phosphate dehydrogenase deficiency is characterized by episodes of hemolytic anemia following oxidative stress (eg, fava beans, dapsone, acute infection). Patients generally have jaundice, dark urine, normocytic anemia, reticulocytosis, and evidence of bite cells and Heinz bodies on peripheral smear.

Pathology	Hematology & Oncology	G6PD deficiency
Subject	System	Topic

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An 18-year-old man with a history of recurrent hemarthroses and severe mucosal bleeding due to hemophilia A comes to the office for follow-up. He has had occasional breakthrough bleeding despite receiving prophylactic factor VIII infusions. Testing reveals the patient now has inhibitor alloantibodies against factor VIII, and factor replacement products can no longer be used. Treatment with a novel medication that prevents bleeding by mimicking the function of factor VIII is initiated. This medication most likely works by which of the following mechanisms?

A. Anchoring platelets to subendothelial collagen
B. Binding factor VIIa to mediate factor X activation
C. Cleaving von Willebrand factor multimers
D. Cross-linking fibrin molecules
E. Linking factors IXa and X to create activated X (Xa)

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An 18-year-old man with a history of recurrent hemarthroses and severe mucosal bleeding due to hemophilia A comes to the office for follow-up. He has had occasional breakthrough bleeding despite receiving prophylactic factor VIII infusions. Testing reveals the patient now has inhibitor alloantibodies against factor VIII, and factor replacement products can no longer be used. Treatment with a novel medication that prevents bleeding by mimicking the function of factor VIII is initiated. This medication most likely works by which of the following mechanisms?

A. ~~Anchoring platelets to subendothelial collagen~~ (8%)

B. ~~Binding factor VIIa to mediate factor X activation~~ (14%)

C. ~~Cleaving von Willebrand factor multimers~~ (6%)

D. ~~Cross-linking fibrin molecules~~ (1%)

✓ E. Linking factors IXa and X to create activated X (Xa) (68%)

Correct

68%
Answered correctly

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Time Spent

10/11/2020
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Hemophilia A is an X-linked, recessive bleeding disorder caused by mutations to the gene that encodes clotting **factor VIII**. Factor VIII is part of the intrinsic coagulation cascade; it acts as a bridging protein that brings together the catalytic component of **factor IXa** (the protease) with **factor X** (the substrate), thereby amplifying formation of factor Xa, which promotes fibrin clots.

Patients with hemophilia A have severe reductions in factor VIII and are unable to form fibrin clots at sites of minor trauma, leading to potentially life-threatening hemarthroses and mucosal bleeding. Treatment with factor VIII replacement products (eg, factor VIII concentrate from plasma) can prevent or treat bleeding in these patients. However, long-term efficacy is often limited by the formation of neutralizing antibodies **(factor VIII inhibitors)**.

Emicizumab, a bispecific monoclonal antibody, mimics the normal physiologic function of factor VIII and can be used to prevent or treat bleeding in patients who have factor VIII inhibitors. This antibody has 2 binding sites; one site binds to factor IXa and the other binds to factor X, which brings them into **close proximity** and allows factor IXa to cleave factor X into its active form (Xa).

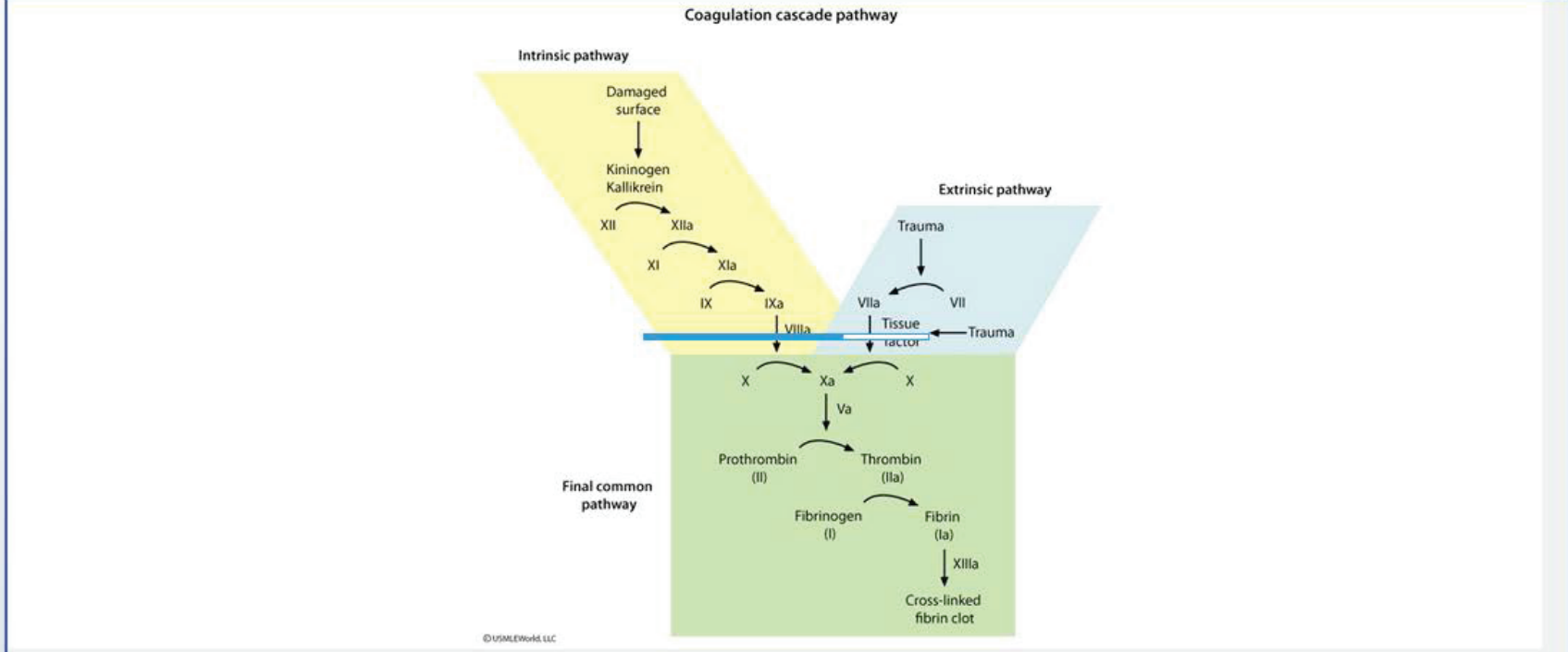
(Choice A) Von Willebrand factor, a large glycoprotein produced by the endothelium, aids platelet clot formation by binding platelets to subendothelial collagen at sites of injury. It is also a carrier protein for factor VIII; therefore, patients with Von Willebrand factor deficiency often have mild or moderate reductions

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Hemophilia A is an X-linked recessive bleeding disorder caused by mutations to the gene that encodes

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formation by binding platelets to subendothelial collagen at sites of injury. It is also a carrier protein for factor VIII; therefore, patients with Von Willebrand factor deficiency often have mild or moderate reductions in factor VIII. However, serious bleeding (eg, hemarthroses) is very uncommon.

(Choice B) Activation of factor X to Xa can also occur via the extrinsic (tissue factor pathway) in response to tissue trauma. In this case, factor VIIa in combination with tissue factor activates factor X. This pathway does not require factor VIII and is unaffected in those with hemophilia A.

(Choice C) Ultra-large von Willebrand factor multimers produced by the endothelium are cleaved to smaller subunits by the metalloprotease ADAMTS13. Loss of ADAMTS13 activity leads to thrombotic thrombocytopenic purpura.

(Choice D) Factor XIIIa cross-links loose fibrin molecules into a dense network, thereby forming stable fibrin clots. Factor XIIIa is unaffected in those with hemophilia A.

Educational objective:
Hemophilia A is an X-linked disorder associated with a deficiency of factor VIII. Emicizumab—a bispecific, monoclonal antibody—mimics the activity of factor VIII by binding to both factor IXa and factor X, bringing them into close proximity to allow for factor X activation.

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A 51-year-old woman comes to the office for a follow-up visit. Three weeks ago, she had a screening mammogram that was suspicious for malignancy. An ultrasound-guided needle aspiration was performed and showed invasive ductal carcinoma. The patient underwent a lumpectomy with axillary dissection and was found to have no metastatic disease. Immunohistochemical analysis of the tumor specimen was significant for the following:

Estrogen receptor	Positive
Progesterone receptor	Positive
Human epidermal growth factor receptor 2	Positive

Adjuvant therapy with a monoclonal antibody is started. Which of the following is the most likely target of this drug?

A. Estrogen receptor
B. Peripheral aromatase enzyme
C. Receptor activator of nuclear factor kappa-B ligand

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was found to have no metastatic disease. Immunohistochemical analysis of the tumor specimen was significant for the following:

Estrogen receptor	Positive
Progesterone receptor	Positive
Human epidermal growth factor receptor 2	Positive

Adjuvant therapy with a monoclonal antibody is started. Which of the following is the most likely target of this drug?

A. Estrogen receptor
B. Peripheral aromatase enzyme
C. Receptor activator of nuclear factor kappa-B ligand
D. Tyrosine kinase receptor
E. Vascular endothelial growth factor

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was found to have no metastatic disease. Immunohistochemical analysis of the tumor specimen was significant for the following:

Estrogen receptor	Positive
Progesterone receptor	Positive
Human epidermal growth factor receptor 2	Positive

Adjuvant therapy with a monoclonal antibody is started. Which of the following is the most likely target of this drug?

A. ~~Estrogen receptor~~ (30%)
B. ~~Peripheral aromatase enzyme~~ (4%)
C. Receptor activator of nuclear factor kappa-B ligand (8%)
✓ D. Tyrosine kinase receptor (48%)
E. Vascular endothelial growth factor (7%)

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This patient has localized invasive ductal **breast carcinoma** that shows estrogen receptor (ER), progesterone receptor (PR), and **human epidermal growth factor receptor 2 (HER2)** positivity. **Trastuzumab** is a monoclonal antibody used in the management of patients with HER2-positive breast cancer. It binds to a portion of the extracellular domain of HER2 and prevents activation of a transmembrane **tyrosine kinase**. This downregulates cellular proliferation and promotes apoptosis. Approximately 20% of all invasive breast cancers overexpress HER2; this can also be found in other solid tumors (eg, stomach, lung, ovary).

(Choices A and B) Hormone receptor-positive breast cancer (ER and/or PR overexpression) is treated with antiestrogen medications to reduce tumor cell proliferation. Premenopausal patients are typically treated with selective estrogen receptor modulators (eg, tamoxifen), while aromatase inhibitors (eg, anastrozole, letrozole) are used in postmenopausal women. However, these medications are not monoclonal antibodies.

(Choice C) Receptor activator of nuclear factor kappa-B ligand (RANKL) activates osteoclasts; RANKL expression on bone may contribute to bone metastases by binding to RANK on tumor cells. Denosumab, a human monoclonal antibody against RANKL, is used to reduce skeletal-related events if metastasis to

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monoclonal antibodies.

(Choice C) Receptor activator of nuclear factor kappa-B ligand (RANKL) activates osteoclasts; RANKL expression on bone may contribute to bone metastases by binding to RANK on tumor cells. Denosumab, a human monoclonal antibody against RANKL, is used to reduce skeletal-related events if metastasis to bone occurs.

(Choice E) Vascular endothelial growth factor (VEGF), which also binds to a tyrosine kinase receptor, induces angiogenesis. VEGF inhibitors, such as the monoclonal antibody bevacizumab, have a role in treatment of some metastatic cancers (eg, colon, lung).

Educational objective:
Human epidermal growth factor receptor 2 (HER2) is a tyrosine kinase receptor that is overexpressed in 20% of breast cancer patients. In such patients, HER2 blockade with the monoclonal antibody trastuzumab downregulates cellular proliferation and promotes apoptosis.

References

- Trastuzumab--mechanism of action and use in clinical practice.
- HER2: biology, detection, and clinical implications.

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A 30-year-old woman comes to the emergency department with sudden-onset abdominal pain and ascites. Laboratory studies show anemia, reticulocytosis, leukopenia, and thrombocytopenia. Flow cytometry of the patient's peripheral blood cells using the appropriate monoclonal antibodies shows CD55 and CD59 deficiency. CT scan of the abdomen shows hepatic vein thrombosis. Which of the following is the most likely cause of this patient's anemia?

A. Complement activation
B. Factor V mutation
C. Intracellular dehydration
D. Mutation in beta globin chain
E. Splenic sequestration

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A 30-year-old woman comes to the emergency department with sudden-onset abdominal pain and ascites. Laboratory studies show anemia, reticulocytosis, leukopenia, and thrombocytopenia. Flow cytometry of the patient's peripheral blood cells using the appropriate monoclonal antibodies shows CD55 and CD59 deficiency. CT scan of the abdomen shows hepatic vein thrombosis. Which of the following is the most likely cause of this patient's anemia?

- ✓ A. Complement activation (64%)
- B. Factor V mutation (10%)
- C. Intracellular dehydration (1%)
- D. Mutation in beta globin chain (4%)
- E. Splenic sequestration (17%)

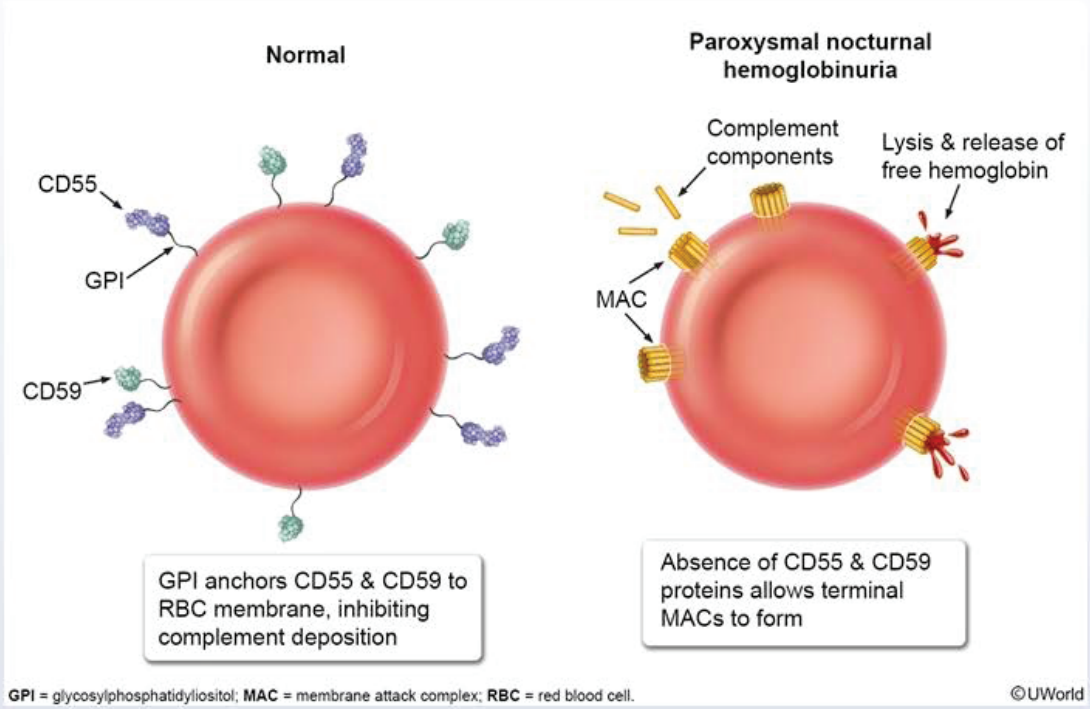
Correct

64%
Answered correctly

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Time Spent

01/26/2021
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This patient's combination of hemolytic anemia, hypercoagulability (eg, hepatic vein thrombosis), and pancytopenia are characteristic of **paroxysmal nocturnal hemoglobinuria (PNH)**. Despite the name

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GPI = glycosylphosphatidyliositol; MAC = membrane attack complex; RBC = red blood cell.

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This patient's combination of hemolytic anemia, hypercoagulability (eg, hepatic vein thrombosis), and pancytopenia are characteristic of **paroxysmal nocturnal hemoglobinuria (PNH)**. Despite the name, hemolysis has been shown to occur at low baseline levels throughout the day, with exacerbations caused by a variety of inflammatory triggers (eg, infections, surgery).

PNH is caused by an acquired mutation of the *PIGA* gene within a clonal population of multipotent hematopoietic stem cells. This gene is involved in the synthesis of the **glycosylphosphatidylinositol (GPI) anchor**, a glycolipid necessary for the attachment of several cell-surface proteins, including CD55 (decay-accelerating factor) and CD59 (MAC inhibitory protein). These proteins help inactivate complement and prevent the membrane attack complex from forming on normal cells.

Absence of the GPI anchor results in CD55 and CD59 deficiency and **complement-mediated hemolysis**. The hemolysis occurs more often at night because complement activity is increased during sleep due to lower blood pH. Patients also develop **thrombotic complications** (eg, Budd-Chiari syndrome), likely due to release of free hemoglobin and other prothrombotic factors from lysed red blood cells and platelets. PNH is often associated with pancytopenia and **aplastic anemia** (possibly due to autoimmune attack against GPI-antigens on stem cells). Flow cytometry is the gold standard for the diagnosis of PNH and will

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show absence of the GPI anchor and **CD55 and CD59 deficiency**.

(Choice B) Factor V mutation can result in an aberration called factor V Leiden, which is resistant to cleavage by activated protein C. Patients with factor V Leiden are at increased risk of thrombotic events, but hemolytic anemia and pancytopenia are not seen.

(Choice C) Intracellular dehydration occurs during the pathogenesis of sickle cell anemia and spherocytosis.

(Choice D) Mutations affecting the beta globin chain cause β-thalassemia.

(Choice E) Splenic sequestration is a common complication of sickle cell anemia.

Educational objective:
The triad of hemolytic anemia, hypercoagulability, and pancytopenia suggests paroxysmal nocturnal hemoglobinuria (PNH). PNH results from an acquired mutation in the *PIGA* gene that causes absence of the glycosylphosphatidylinositol anchor and associated deficiency of CD55 and CD59 complement inhibitor proteins.

References

- The phenotype of a germline mutation in PIGA: the gene somatically mutated in paroxysmal nocturnal

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A 60-year-old African-American female is evaluated for fatigue. Past surgical history includes mitral valve repair with a mechanical valve due to severe mitral insufficiency. She has 30-pack year history of smoking and occasionally drinks alcohol. Examination shows pallor. Laboratory studies show the following:

Complete blood count

Hemoglobin	9.0 g/L
Reticulocytes	6.8%
Platelets	218,000/mm^3
Leukocyte count	4,500/mm^3

Serum chemistries are within normal limits. Her peripheral smear shows red blood cell fragments, "burr cells," and "helmet cells". Which of the following is the most likely cause of her condition?

A. Microvascular thrombi

B. Cytoskeleton abnormality

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Hemoglobin	9.0 g/L
Reticulocytes	6.8%
Platelets	218,000/mm^3
Leukocyte count	4,500/mm^3

Serum chemistries are within normal limits. Her peripheral smear shows red blood cell fragments, "burr cells," and "helmet cells". Which of the following is the most likely cause of her condition?

A. Microvascular thrombi
B. Cytoskeleton abnormality
C. Impaired DNA synthesis
D. Gastrointestinal blood loss
E. Mutation in beta globin chain
F. Complement mediated hemolysis

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Leukocyte count	4,500/mm^3

Serum chemistries are within normal limits. Her peripheral smear shows red blood cell fragments, "burr cells," and "helmet cells". Which of the following is the most likely cause of her condition?

A. Microvascular thrombi (6%)
B. Cytoskeleton abnormality (3%)
C. Impaired DNA synthesis (1%)
D. Gastrointestinal blood loss (1%)
E. Mutation in beta globin chain (3%)
F. Complement mediated hemolysis (3%)
G. Mechanical trauma (80%)

Correct

80%
Answered correctly

54 secs
Time Spent

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All of the choices represent mechanisms for anemia. The key to answering this question is this patient's history and peripheral smear. Red blood cell fragments, burr cells and helmet cells are consistent with traumatic hemolysis, which can result from either microangiopathic hemolytic anemia or mechanical damage (e.g. prosthetic valve).

Prosthetic valves produce excessive shear and turbulence in the cardiac circulation, causing mechanical trauma to the RBCs.

Burr cells are erythrocytes with short, evenly-spaced projections. They can occur as an artifact or in association with uremia, pyruvate kinase deficiency, microangiopathic hemolytic anemia, or mechanical damage.

(Choice A) Microvascular thrombi are the pathophysiologic mechanism for microangiopathic hemolytic anemia, which causes thrombocytopenia. In this patient, platelet count is normal.

(Choice B) Cytoskeleton abnormalities describe an intracorpuscular defect characteristic of a group of anemias that includes hereditary spherocytosis, hereditary elliptocytosis, and hereditary stomatocytosis. Respectively, spherocytes, elliptocytes, or stomatocytes are characteristically seen in the peripheral blood smear.

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shear.

(Choice C) Impaired DNA synthesis is the pathophysiologic mechanism for megaloblastic anemia. Ovalocytes are the associated morphologic RBC variant seen in this group of anemia. In addition, hypersegmented neutrophils are also characteristic.

(Choice D) Gastrointestinal blood loss results in hypochromic, microcytic anemia due to iron deficiency.

(Choice E) Mutation of the beta globin chain results in beta thalassemia; target cells are the RBC morphologic variant commonly seen.

(Choice F) Paroxysmal nocturnal hemoglobinuria is an episodic hemolysis caused by a complement-mediated mechanism. Leukopenia and thrombocytopenia (pancytopenia) are commonly associated.

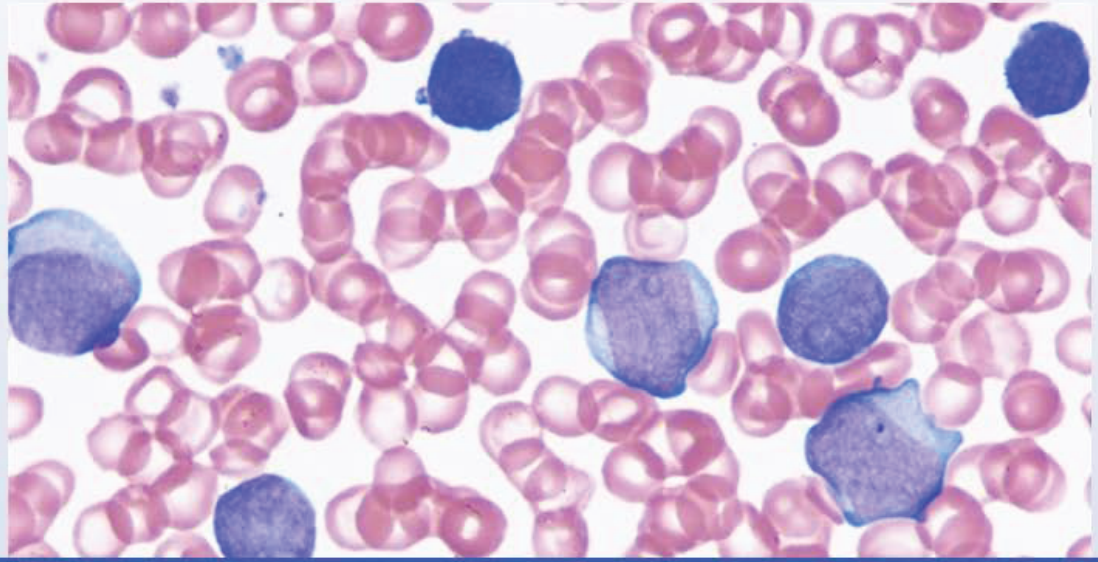
Educational Objective:

- Red blood cell fragments, burr cells, and helmet cells are associated with either microangiopathic hemolytic anemia or mechanical red cell destruction.
- In patients with prosthetic valves, red blood cells are exposed to excessive shear and turbulence in the circulation, causing damage from mechanical trauma.

Pathology Hematology & Oncology Hemolytic anemia

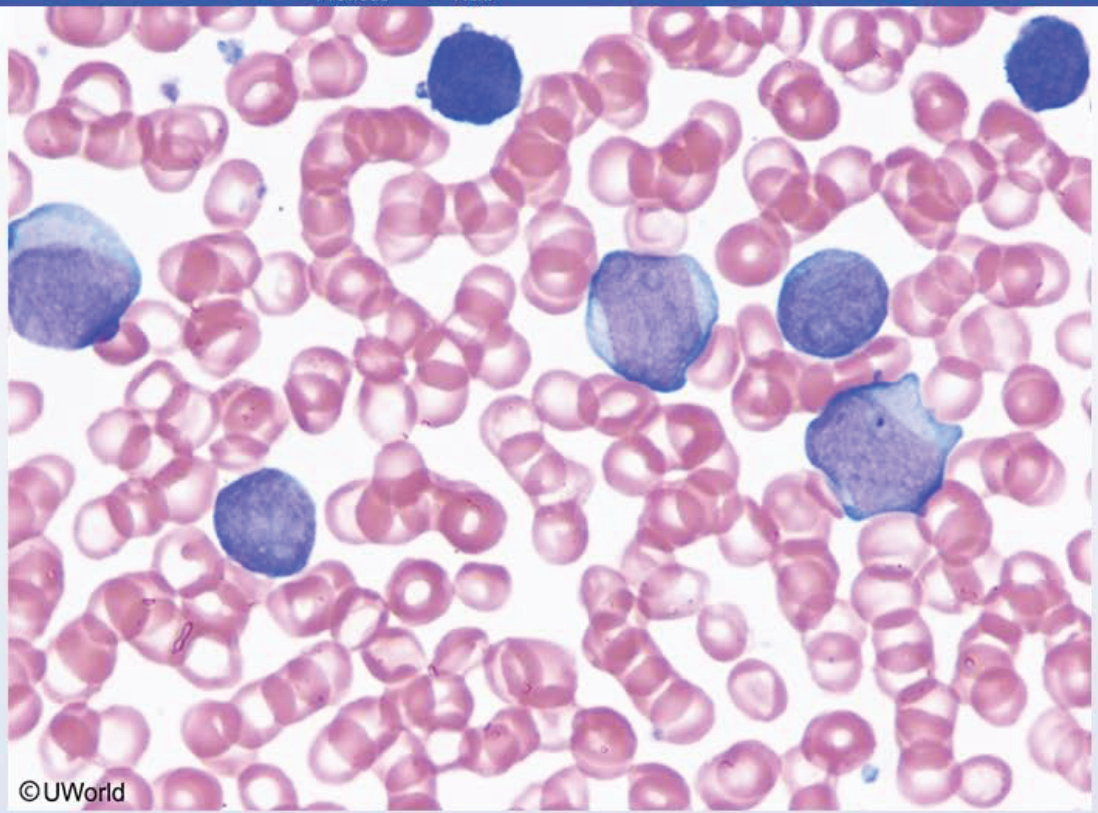
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A 15-year-old previously healthy patient arrives at the emergency department due to progressive shortness of breath. Chest x-ray shows a large mediastinal mass and bilateral pleural effusions. Leukocyte count is elevated, and peripheral blood smear reveals abnormal white blood cells, as shown below. These cells are positive for terminal deoxynucleotidyl transferase and CD3 and negative for CD19. Which of the following is the most likely diagnosis?



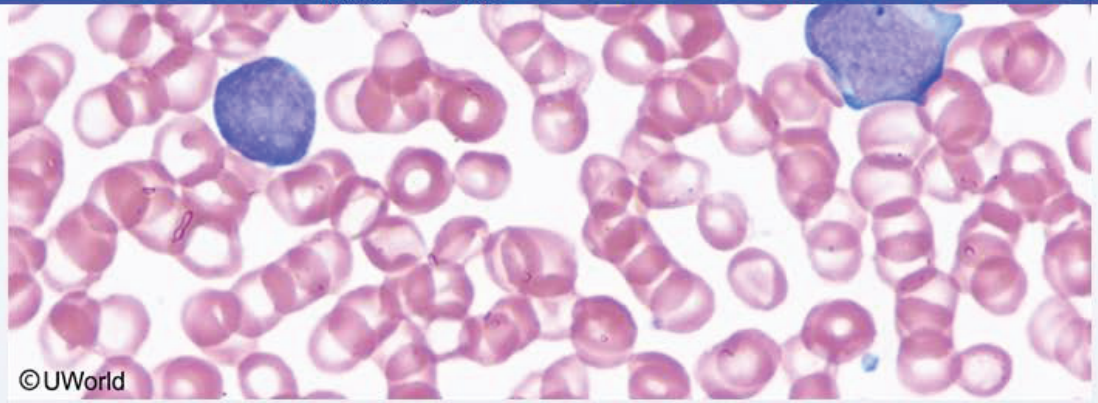
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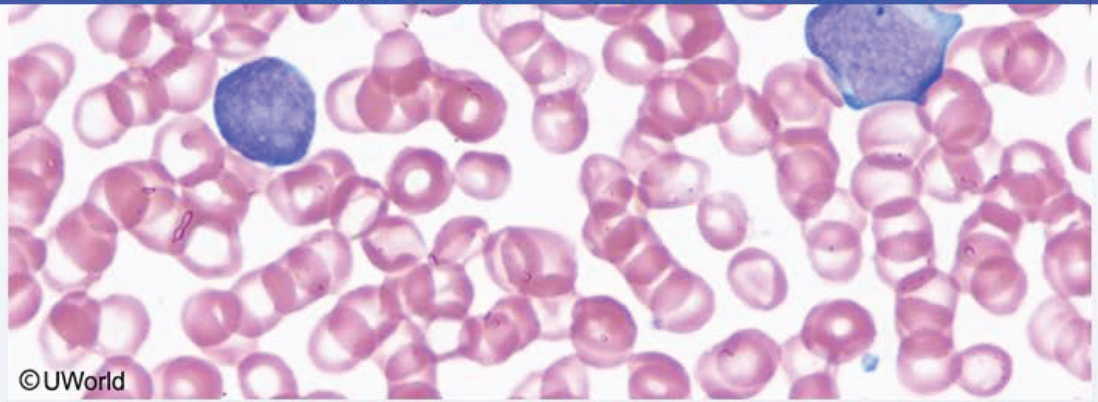


A. Acute lymphoblastic leukemia
B. Acute myeloid leukemia
C. Burkitt lymphoma
D. Hodgkin lymphoma
E. Mantle cell lymphoma

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A. Acute lymphoblastic leukemia (83%)
B. Acute myeloid leukemia (5%)
C. Burkitt lymphoma (2%)
D. Hodgkin lymphoma (3%)
E. Mantle cell lymphoma (4%)

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This patient's peripheral blood smear demonstrates blast cells with large, irregular nuclei and granular chromatin. Blast cells are early hematologic precursors that may be either lymphoid or myeloid in origin. The presence of **terminal deoxynucleotidyl transferase** (TDT), a DNA polymerase involved in V(D)J recombination that is expressed only by lymphoid progenitor cells, indicates that the cells are lymphoblasts. Lymphoblasts are then further differentiated by the presence or absence of specific surface markers unique to B cells (eg, CD19, CD20) or T cells (eg, **CD3**).

This patient with circulating blasts that are positive for TDT (indicating lymphoid origin) and CD3 (indicating T-cell origin) has **T-cell acute lymphoblastic leukemia** (ALL). Unlike B-cell ALL, which usually occurs in early childhood, **T-cell ALL** is most common in the **teenage years** or early adulthood. Tumors classically develop in the thymus, the organ charged with T-cell development, and often result in the formation of a **mediastinal mass** that compresses the airway (causing cough and dyspnea) or nearby blood vessels (causing superior vena cava syndrome). Pleural effusions are also common due to inflammation from tumor growth/cytokine release.

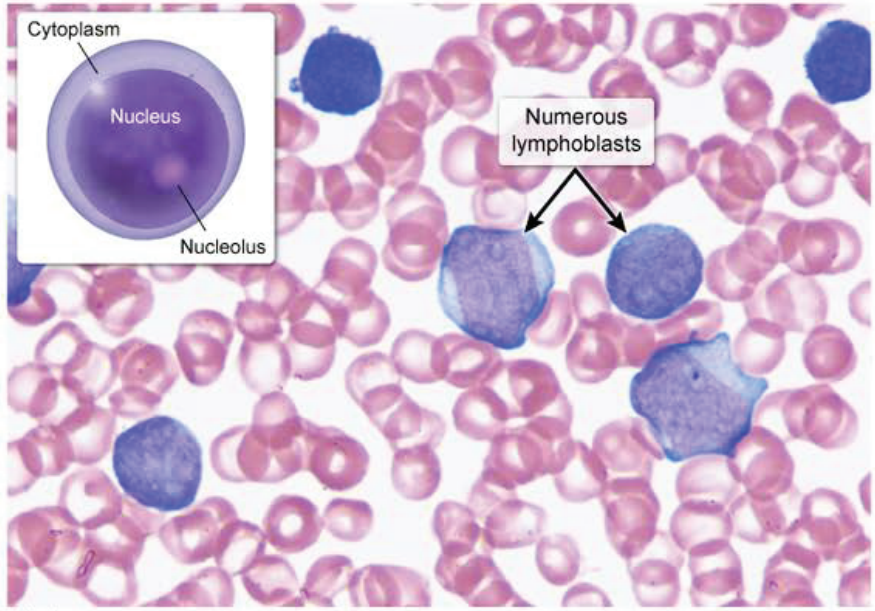
(Choice B) Acute myeloid leukemia is a hematologic malignancy that arises from myeloid precursors. Although myeloblasts can occasionally be confused with lymphoblasts, myeloblasts never express TDT.

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Exhibit Display

Acute lymphoblastic leukemia



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(Choice B) Acute myeloid leukemia is a hematologic malignancy that arises from myeloid precursors. Although myeloblasts can occasionally be confused with lymphoblasts, myeloblasts never express TDT. Auer rods are a specific finding in myeloblastic leukemia.

(Choice C) Burkitt lymphoma is an aggressive B-cell, non-Hodgkin lymphoma that is strongly associated with Epstein-Barr virus. Jaw/facial bone and abdominal involvement are common; a mediastinal mass would be atypical. In addition, Burkitt lymphoma cells express B-cell, not T-cell, tumor markers and are not associated with circulating blasts.

(Choice D) Hodgkin lymphoma is a neoplasm that arises from germinal or post-germinal center B cells. Most patients have painless, peripheral lymphadenopathy, particularly in the cervical region. Reed-Sternberg cells (large lymphocytes with multiple or bilobed nuclei and eosinophilic nucleoli) are characteristically seen in bone marrow. Circulating blasts are not a typical feature of this disease, and cells would express B-cell, not T-cell, markers.

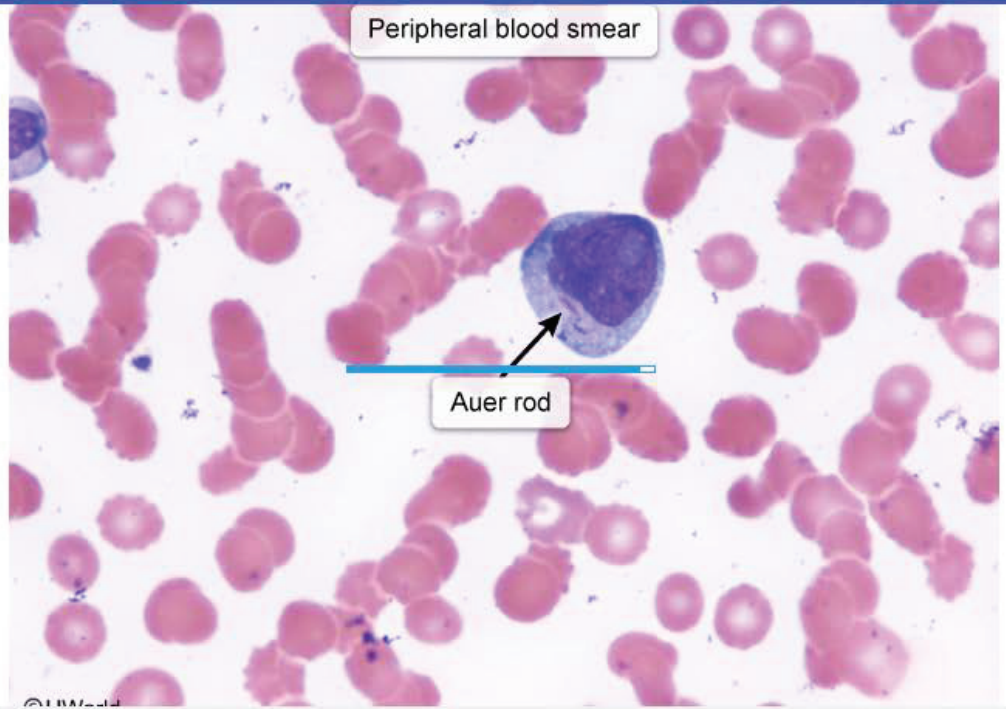
(Choice E) Mantle cell lymphoma is a mature B-cell, non-Hodgkin lymphoma that usually presents with lymphadenopathy, splenomegaly, and cytopenia. This tumor type would express B-cell, not T-cell, surface markers, and peripheral blasts would be atypical.

Educational objective:

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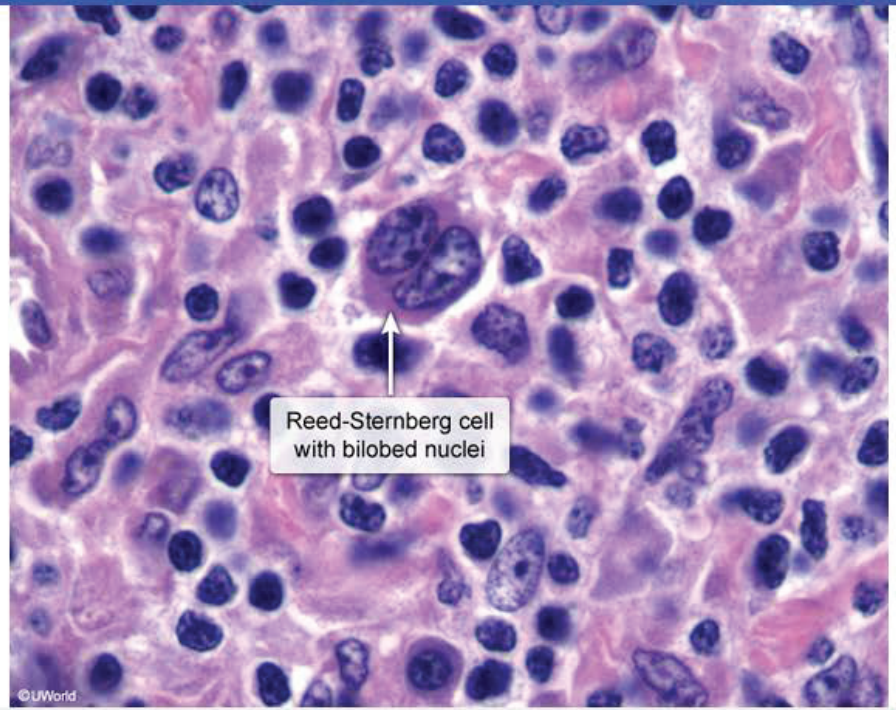
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Educational objective:

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Educational objective:

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(Choice D) Hodgkin lymphoma is a neoplasm that arises from germinal or post-germinal center B cells. Most patients have painless, peripheral lymphadenopathy, particularly in the cervical region. Reed-Sternberg cells (large lymphocytes with multiple or bilobed nuclei and eosinophilic nucleoli) are characteristically seen in bone marrow. Circulating blasts are not a typical feature of this disease, and cells would express B-cell, not T-cell, markers.

(Choice E) Mantle cell lymphoma is a mature B-cell, non-Hodgkin lymphoma that usually presents with lymphadenopathy, splenomegaly, and cytopenia. This tumor type would express B-cell, not T-cell, surface markers, and peripheral blasts would be atypical.

Educational objective:

Acute lymphoblastic leukemia (ALL) is marked by a high concentration of circulating lymphoblasts. Flow cytometry can be used to distinguish between B-cell (CD19-expressing) and T-cell (CD3-expressing) lineages. T-cell ALL usually arises in teenagers or individuals in their 20s and often presents with a large mediastinal mass.

Pathology	Hematology & Oncology	Acute lymphoblastic leukemia
Subject	System	Topic

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A 7-year-old African American boy is brought to the office by his parents. The parents state that the boy has been hospitalized several times for severe pains in his back and extremities. The patient is very active when he is not in pain but gets quite tired by the end of the day. He has no other medical problems and takes no medications except acetaminophen for pain control. On examination, the conjunctivae are pale. Blood count reveals a hemoglobin level of 7.8 mg/dL and a reticulocyte count of 15%. A valine for glutamic acid substitution at position 6 of the β globin chain of the hemoglobin molecule is suspected. This patient's hemoglobin would most likely aggregate upon which of the following?

A. 2,3-bisphosphoglycerate depletion
B. β globin chain folding
C. Capillary pH values >7.4
D. Interaction with fetal hemoglobin
E. Oxygen unloading

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A. 2,3-bisphosphoglycerate depletion (11%)
B. ~~β globin chain folding~~ (9%)
C. ~~Capillary pH values >7.4~~ (5%)
D. ~~Interaction with fetal hemoglobin~~ (4%)
E. Oxygen unloading (68%)

68%
55 secs
12/18/2020

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In **sickle cell (hemoglobin S [HbS]) anemia**, the nonpolar amino acid valine replaces the charged amino acid glutamate at position 6 of the β globin chain. This results in the alteration of a hydrophobic portion of the β globin chain that fits into a complementary site on the α globin chain of another hemoglobin molecule. As a result, hemoglobin molecules aggregate under anoxic conditions. After polymerization, HbS initially forms a gel and then a meshwork of fibrous polymers causing the red blood cells to distort into an abnormal sickle shape.

Sickling is promoted by conditions associated with **low oxygen** levels, increased acidity, or low blood volume (dehydration). Sickled cells are not flexible enough to pass through microvasculature. As a result, they impede blood flow and cause microinfarcts in tissues and painful vasoocclusive crises. Organs in which blood moves slowly (eg, spleen, liver) are predisposed to lower oxygen levels or acidity. Organs with particularly high metabolic demands (eg, brain, muscles, placenta) promote sickling by extracting more oxygen from the blood (**oxygen unloading**). The sickling process is complex and incompletely understood.

(Choices A and C) The molecule 2,3-bisphosphoglycerate (2,3-BPG) binds the 2 β globin chains ionically and stabilizes the taut (T) deoxyhemoglobin. This binding decreases hemoglobin's oxygen affinity, facilitating oxygen release at the tissue level. With 2,3-BPG depletion, hemoglobin affinity for oxygen

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(Choices A and C) The molecule 2,3-bisphosphoglycerate (2,3-BPG) binds the 2 β globin chains ionically and stabilizes the taut (T) deoxyhemoglobin. This binding decreases hemoglobin's oxygen affinity, facilitating oxygen release at the tissue level. With 2,3-BPG depletion, hemoglobin affinity for oxygen increases (left shift on oxygen-hemoglobin dissociation curve), and this results in oxygen uptake by hemoglobin; therefore, erythrocyte sickling will decrease. Similarly, increased acidity or low pH is associated with sickling, so decreased acidity with elevated capillary pH values >7.4 would not promote sickling.

(Choice B) The globin chains in the hemoglobin tetramer are folded compactly, with nonpolar hydrophobic residues in the interior and charged polar residues on the surface. A valine for glutamic acid substitution does not result in a significant change in β globin folding. It is the mature hemoglobin tetramer that undergoes polymerization, not individual globin chains during folding.

(Choice D) HbS does not polymerize when fetal hemoglobin (HbF) is present, so patients with sickle cell

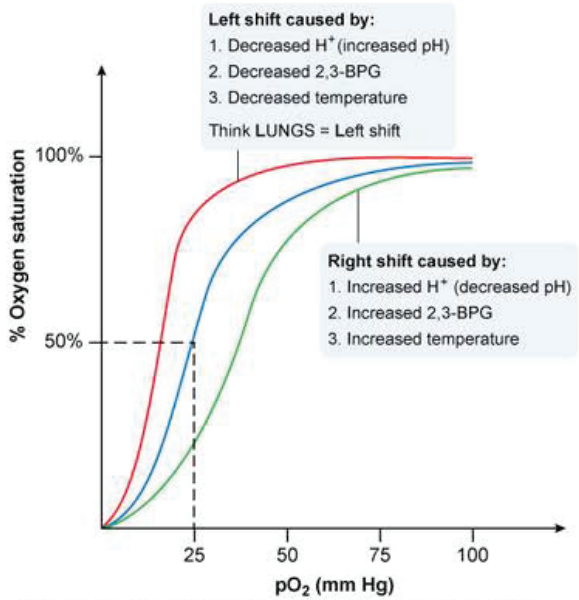
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which blood moves slowly (eg, spleen, liver) are predisposed to lower oxygen levels or acidity. Organs with

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Oxygen-hemoglobin dissociation curve



2,3-BPG = 2,3-bisphosphoglycerate; pO_2 = partial pressure of oxygen in the blood.

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residues in the interior and charged polar residues on the surface. A valine for glutamic acid substitution does not result in a significant change in β globin folding. It is the mature hemoglobin tetramer that undergoes polymerization, not individual globin chains during folding.

(Choice D) HbS does not polymerize when fetal hemoglobin (HbF) is present, so patients with sickle cell anemia often do not have symptoms until the HbF fraction decreases a few months after delivery. Some patients with HbS may have fewer clinical manifestations because they produce larger amounts of HbF as adults.

Educational objective:

Hemoglobin S (HbS) aggregates in the deoxygenated state. HbS polymers form fibrous strands that reduce red blood cell membrane flexibility and promote sickling. Sickling occurs under conditions associated with anoxia including low pH and high levels of 2,3-bisphosphoglycerate. These inflexible erythrocytes predispose to microvascular occlusion and microinfarcts.

References

- Newer aspects of the pathophysiology of sickle cell disease vaso-occlusion.
- Sickle cell anemia, the first molecular disease: overview of molecular etiology, pathophysiology, and therapeutic approaches.

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Certain patients with non-small cell lung cancer develop constitutive tumor kinase activity due to the production of echinoderm microtubule-associated protein-like 4 - anaplastic lymphoma kinase (EML4-ALK), a fusion protein that contributes to carcinogenesis. This is most similar to the molecular pathophysiology of which of the following disorders?

A. Burkitt lymphoma
B. Chronic myelogenous leukemia
C. Follicular lymphoma
D. Li-Fraumeni syndrome
E. Mantle cell lymphoma

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Certain patients with non-small cell lung cancer develop constitutive tumor kinase activity due to the production of echinoderm microtubule-associated protein-like 4 - anaplastic lymphoma kinase (EML4-ALK), a fusion protein that contributes to carcinogenesis. This is most similar to the molecular pathophysiology of which of the following disorders?

A. Burkitt lymphoma (11%)
B. Chronic myelogenous leukemia (66%)
C. Follicular lymphoma (8%)
D. Li-Fraumeni syndrome (8%)
E. Mantle cell lymphoma (5%)

Correct

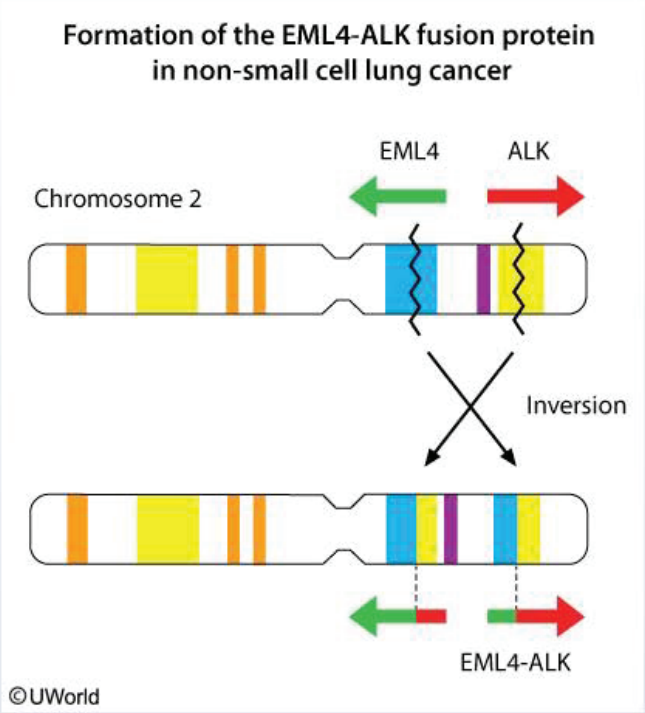
66%
Answered correctly

40 secs
Time Spent

11/15/2020
Last Updated

Explanation

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Approximately four percent of patients with non-small cell lung carcinoma (NSCLC) have an inversion of the short arm of chromosome 2 that creates a fusion gene between EML4 (echinoderm microtubule-

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Approximately four percent of patients with non-small cell lung carcinoma (NSCLC) have an inversion of the short arm of chromosome 2 that creates a fusion gene between EML4 (echinoderm microtubule-associated protein-like 4) and ALK (anaplastic lymphoma kinase). This results in a constitutively active tyrosine kinase that causes malignancy. Interestingly, patients who harbor this gene fusion are usually young non-smokers, often with adenocarcinoma, who lack mutations in either the epidermal growth factor receptor gene or the K-ras gene. The kinase activity of this fusion protein is a target of the protein kinase inhibitor, crizotinib.

The pathophysiology of EML4-ALK NSCLC is most similar to the pathophysiology of chronic myelogenous leukemia (CML). In CML, the classic and most common cause is a translocation between chromosomes 9 and 22. The ABL proto-oncogene is transported from chromosome 9 to chromosome 22 where it is placed adjacent to the BCR gene. The resulting oncogene, BCR-ABL, codes for a fusion protein with constitutive tyrosine kinase activity. This protein stimulates the proliferation of granulocytic precursors and leads to the development of CML. The kinase activity of this fusion protein is a target of the protein kinase inhibitor, imatinib.

(Choice A) Burkitt lymphoma is characterized by a translocation of the c-myc oncogene on the long arm of chromosome 8 to the Ig heavy chain region on chromosome 14. This causes constitutive overproduction of

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(Choice A) Burkitt lymphoma is characterized by a translocation of the c-myc oncogene on the long arm of chromosome 8 to the Ig heavy chain region on chromosome 14. This causes constitutive overproduction of c-myc, a nuclear phosphoprotein that functions as a transcription activator.

(Choice C) Patients with follicular lymphoma have a t(14;18) translocation that causes overexpression of the antiapoptotic BCL2 gene product.

(Choice D) Li-Fraumeni syndrome is an autosomal dominant predisposition to a variety of cancers, particularly sarcomas and tumors of the breast, brain, and adrenal cortex. This syndrome is associated with a mutation of the tumor suppressor gene, p53.

(Choice E) Translocation between the cyclin D1 locus on chromosome 11 and the immunoglobulin heavy chain locus on chromosome 14 is characteristic of mantle cell lymphoma. This abnormality results in increased production of cyclin D1, a promoter of the G1 to S-phase transition during the cell cycle.

Educational objective:
Some patients with non-small cell lung carcinoma (NSCLC) harbor a chromosomal rearrangement that creates a fusion gene between EML4 (echinoderm microtubule-associated protein-like 4) and ALK (anaplastic lymphoma kinase). This results in a constitutive active tyrosine kinase that causes malignancy.

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A 28-year-old African American man is given prophylactic medications and vaccinations before a business trip to Africa. Five days later, he comes to the emergency department due to jaundice and dark urine. Laboratory results are as follows:

Hemoglobin	8.2 g/dL
Reticulocytes	8.0%
Total bilirubin	3.5 mg/dL
Direct bilirubin	1.1 mg/dL
Lactate dehydrogenase	342 U/L
Haptoglobin	42 mg/dL (normal: 50-150 mg/dL)

A peripheral smear shows red blood cells with dark inclusions when stained with supravital stain. This patient's condition most likely has which of the following inheritance patterns?

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Direct bilirubin	1.1 mg/dL
Lactate dehydrogenase	342 U/L
Haptoglobin	42 mg/dL (normal: 50-150 mg/dL)

A peripheral smear shows red blood cells with dark inclusions when stained with supravital stain. This patient's condition most likely has which of the following inheritance patterns?

- A. Autosomal dominant inheritance
- B. Autosomal recessive inheritance
- C. Mitochondrial inheritance
- D. X-linked dominant inheritance
- E. X-linked recessive inheritance

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Lactate dehydrogenase	342 U/L
Haptoglobin	42 mg/dL (normal: 50-150 mg/dL)

A peripheral smear shows red blood cells with dark inclusions when stained with supravital stain. This patient's condition most likely has which of the following inheritance patterns?

- A. Autosomal dominant inheritance (7%)
- B. Autosomal recessive inheritance (31%)
- C. Mitochondrial inheritance (1%)
- D. X-linked dominant inheritance (3%)
- ✓ E. X-linked recessive inheritance (57%)

Correct

57%
Answered correctly

46 secs
Time Spent

01/17/2021
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This patient has the classic history of hemolytic anemia due to medication-induced oxidative stress. The antimalarial drugs usually prescribed for travelers to affected regions (eg, certain parts of Africa) are notorious instigators of **hemolysis** in individuals with **glucose-6-phosphate dehydrogenase (G6PD) deficiency**. Laboratory studies reflect intravascular and extravascular hemolysis with anemia, reticulocytosis, indirect hyperbilirubinemia, and low haptoglobin (due to the removal of free hemoglobin-haptoglobin complexes). Peripheral blood smear shows red blood cells with **Heinz bodies**, dark, intracellular inclusions that stain with supravital stain and represent hemoglobin that has denatured/precipitated from oxidative stress. Heinz bodies are strongly associated with G6PD deficiency and other unstable hemoglobinopathies.

The expression of G6PD is determined by a gene located on the X chromosome and has **X-linked recessive** inheritance. Among individuals with the mutation, males are affected and females are generally carriers.

(Choices A and B) Most structural abnormalities follow an autosomal dominant pattern, whereas most enzyme deficiencies follow an autosomal recessive pattern. For example, hereditary spherocytosis is most often autosomal dominant.

(Choice C) In a zygote, all of the mitochondria are inherited from the mother. These mitochondria have a

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carriers.

(Choices A and B) Most structural abnormalities follow an autosomal dominant pattern, whereas most enzyme deficiencies follow an autosomal recessive pattern. For example, hereditary spherocytosis is most often autosomal dominant.

(Choice C) In a zygote, all of the mitochondria are inherited from the mother. These mitochondria have a small genome, so defects are transmitted only from mothers but affect offspring of both genders. Mitochondrial diseases generally affect oxidative phosphorylation (eg, Leber hereditary optic neuropathy).

(Choice D) In X-linked dominant inheritance, there is 100% risk to female offspring of an affected male. For example, vitamin D-resistant rickets has an X-linked dominant inheritance pattern.

Educational objective:
Glucose-6-phosphate dehydrogenase deficiency has an X-linked recessive inheritance. Hereditary spherocytosis follows an autosomal dominant inheritance pattern.

Pathology	Hematology & Oncology	G6PD deficiency
Subject	System	Topic

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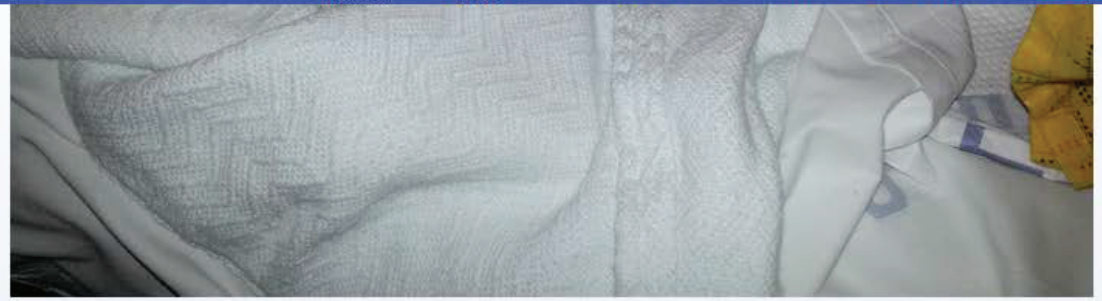
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A 50-year-old man comes to the emergency department due to a large, painful skin lesion. He does not remember sustaining any trauma. He was recently diagnosed with atrial fibrillation, for which warfarin was begun. The patient noticed the lesion about 36 hours after starting the medication. Temperature is 36.7 C (98 F), blood pressure is 130/82 mm Hg, and pulse is 88/min and irregularly irregular. Physical examination findings are shown in the image below.



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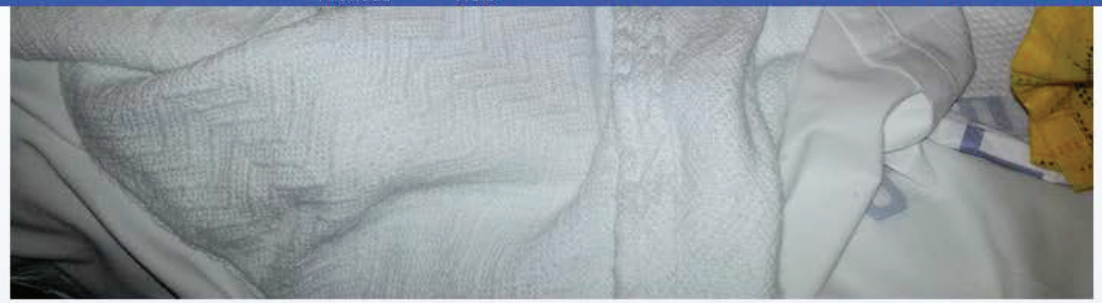
The remainder of the skin examination is normal. Which of the following is the most likely cause of this patient's skin lesion?

A. Allergic drug reaction
B. Antithrombin deficiency
C. Autoimmune phenomena
D. Protein C deficiency
E. Vitamin K deficiency

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The remainder of the skin examination is normal. Which of the following is the most likely cause of this patient's skin lesion?

A. Allergic drug reaction (7%)
B. Antithrombin deficiency (3%)
C. Autoimmune phenomena (4%)
D. Protein C deficiency (73%)
E. Vitamin K deficiency (10%)

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Explanation

This patient was started on warfarin to prevent thromboembolism secondary to atrial fibrillation. The sharply demarcated purpuric lesion likely represents **warfarin-induced skin necrosis**, a rare complication that can occur in individuals with underlying **protein C or S deficiency** shortly after starting warfarin.

Protein C and S are innate anticoagulants that are vitamin K dependent, as are coagulation factors II, VII, IX, and X. Warfarin inhibits epoxide reductase (responsible for regenerating vitamin K), which leads to decreased levels of these proteins. Factor VII and protein C are depleted first due to their shorter half-life. The early loss of protein C leads to a **transient hypercoagulable state** that persists until the other coagulant factors are sufficiently inhibited. In patients with protein C or S deficiency, this prothrombotic state is exaggerated, promoting **microvasculature occlusion** and hemorrhagic skin necrosis.

Treatment of warfarin-induced skin necrosis includes discontinuing warfarin and administering fresh frozen plasma or protein C concentrate.

(Choice A) Allergic drug reactions are immune-mediated hypersensitivity reactions that can have variable cutaneous findings ranging from diffuse erythematous eruptions to extensive blistering and exfoliation (eg, Stevens-Johnson syndrome/toxic epidermal necrolysis). However, this patient's recent warfarin use and localized skin findings are more suggestive of warfarin-induced skin necrosis.

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localized skin findings are more suggestive of warfarin-induced skin necrosis.

(Choice B) Antithrombin deficiency can be inherited (autosomal dominant) or acquired (eg, cirrhosis, nephrotic syndrome) and presents with venous thromboembolism (eg, deep vein thrombosis, pulmonary embolism) and resistance to heparin.

(Choice C) Heparin-induced thrombocytopenia is an autoimmune phenomenon that causes arterial and venous thrombosis. It can produce skin findings similar to this patient's but would generally be associated with thrombocytopenia and recent heparin use.

(Choice E) Vitamin K deficiency is usually associated with easy bruising and bleeding, although thrombosis could potentially occur in patients with concomitant protein C deficiency. However, vitamin K deficiency most often occurs in patients who have fat malabsorption or those who are taking broad-spectrum antibiotics.

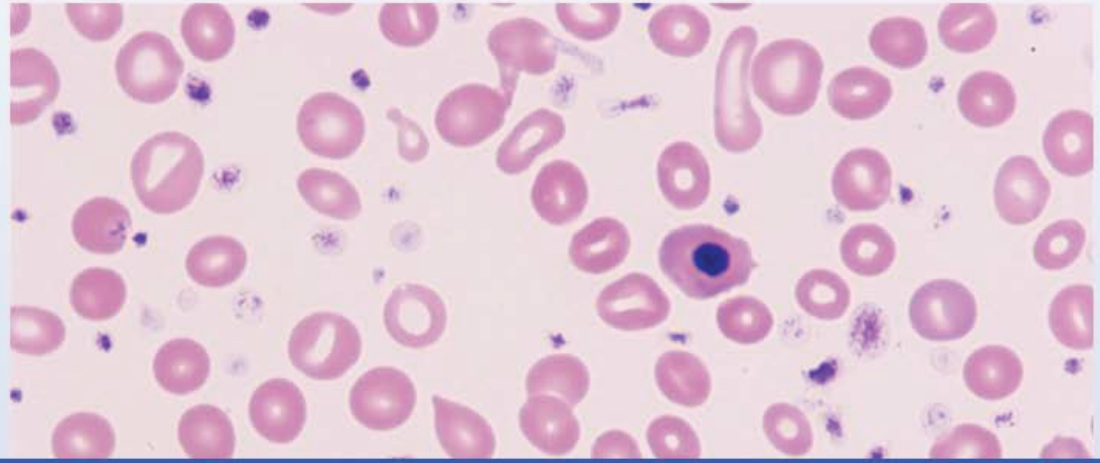
Education objective:

Patients started on warfarin develop a transient hypercoagulable state due to the short half-life of protein C. This hypercoagulability is further exaggerated by preexisting protein C deficiency and can result in thrombotic occlusion of the microvasculature with skin necrosis.

References

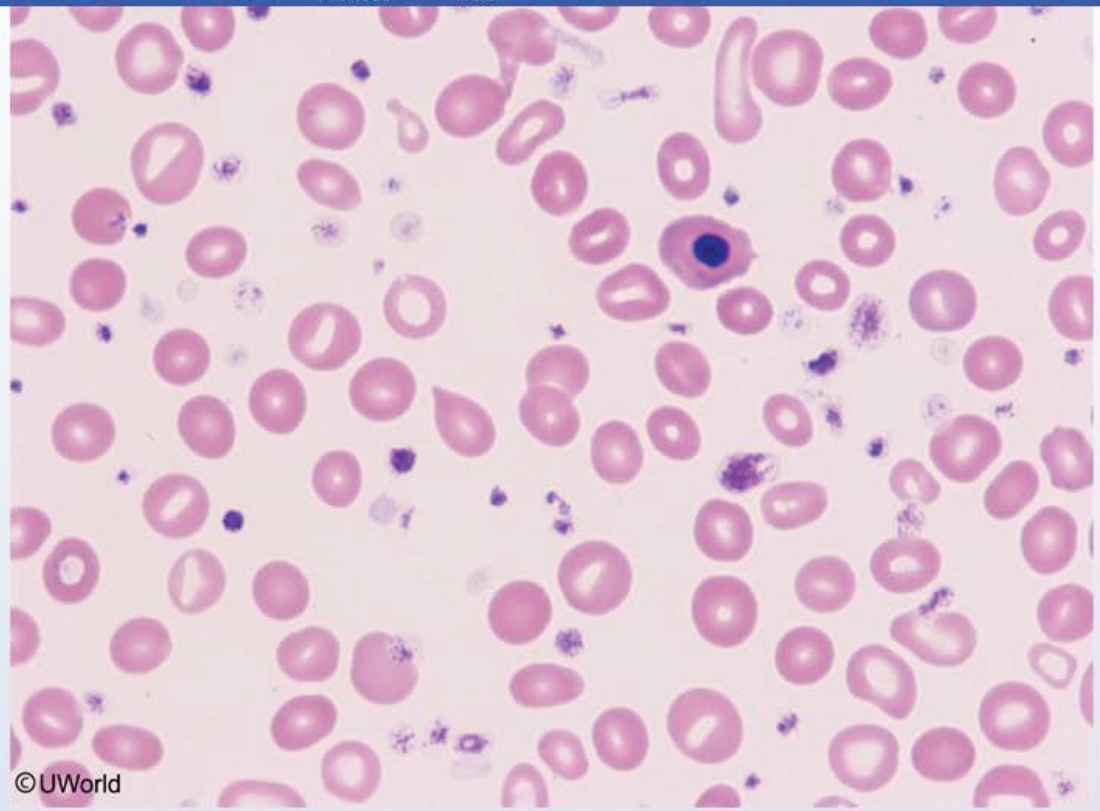
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A 68-year-old man comes to the office with a few months of severe fatigue and a 6.8-kg (15-lb) unintentional loss in weight. The patient has no significant medical history and has not seen a physician in many years. He takes no medications and does not use tobacco, alcohol, or illicit drugs. Physical examination shows mucosal pallor with no scleral icterus. The lungs are clear on auscultation, and heart sounds are normal. Abdominal examination shows mild hepatomegaly and a markedly enlarged spleen. Stool guaiac testing is negative. Laboratory results show pancytopenia, and peripheral blood smear is shown below.



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Bone marrow aspiration is attempted but yields no marrow, and a bone marrow biopsy is subsequently

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Bone marrow aspiration is attempted but yields no marrow, and a bone marrow biopsy is subsequently performed. Which of the following findings is most likely to be observed in this patient's bone marrow?

A. Diffusely fibrotic marrow with clusters of megakaryocytes
B. Hypercellular marrow composed of clusters of plasma cells
C. Increased staining for storage iron in marrow macrophages
D. Marrow replaced by dysplastic cells of all 3 lineages
E. Severely hypocellular marrow replaced by adipose cells

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Bone marrow aspiration is attempted but yields no marrow, and a bone marrow biopsy is subsequently performed. Which of the following findings is most likely to be observed in this patient's bone marrow?

- A. Diffusely fibrotic marrow with clusters of megakaryocytes (61%)
- B. ~~Hypercellular marrow composed of clusters of plasma cells~~ (3%)
- C. ~~Increased staining for storage iron in marrow macrophages~~ (1%)
- D. ~~Marrow replaced by dysplastic cells of all 3 lineages~~ (7%)
- E. Severely hypocellular marrow replaced by adipose cells (26%)

Correct

61%

03 mins, 35 secs

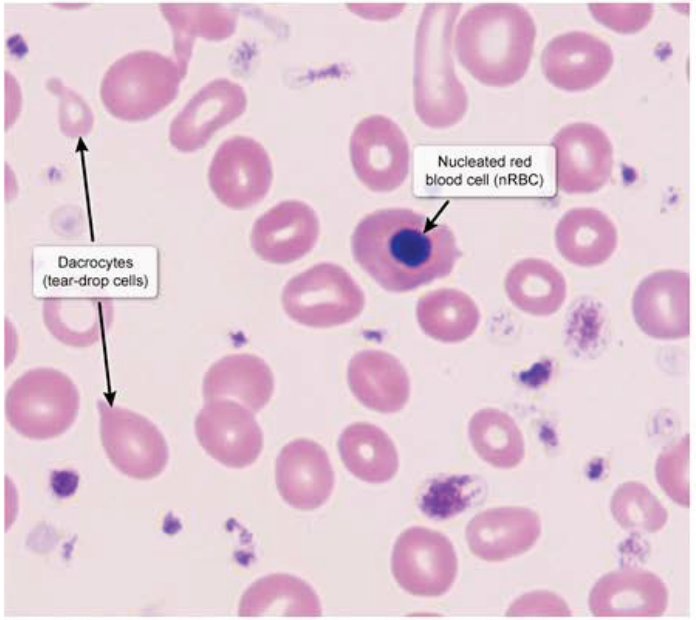
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Exhibit Display

Primary myelofibrosis



Dacrocytes and nRBCs indicate inefficient/extramedullary hematopoiesis (eg, spleen) due to bone marrow destruction.

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This patient with pancytopenia, hepatosplenomegaly, and teardrop cells on peripheral blood smear likely has **primary myelofibrosis**, a hematopoietic stem cell malignancy associated with the clonal expansion of **megakaryocytes**. Neoplastic megakaryocytes secrete the cytokine **transforming growth factor-beta**, which stimulates bone marrow fibroblasts to fill the medullary space with collagen. Subsequent **bone marrow fibrosis** usually leads to the following:

- **Extramedullary hematopoiesis** – Because the bone marrow is destroyed by fibrotic tissue, hematopoiesis occurs in secondary hematopoietic tissue such as the spleen and liver. This typically results in **marked splenomegaly** and a palpable liver edge on examination.
- **Cytopenias** – Extramedullary hematopoiesis is much less efficient than medullary hematopoiesis. Therefore, patients often have deficits in 1 (eg, anemia) or more (eg, **pancytopenia**) cell lines.
- **Dacrocytes** on peripheral blood smear – The red cell membrane is damaged when squeezing out of the fibrotic bone marrow or passing through the enlarged spleen, which leads to the formation of teardrop-shaped red cells.

The diagnosis of primary myelofibrosis requires bone marrow examination. Bone marrow aspiration frequently results in a "**dry tap**" (no marrow) due to significant bone marrow fibrosis. Therefore, bone marrow biopsy is usually required; the presence of a diffusely fibrotic marrow with occasional clusters of atypical megakaryocytes confirms the diagnosis.

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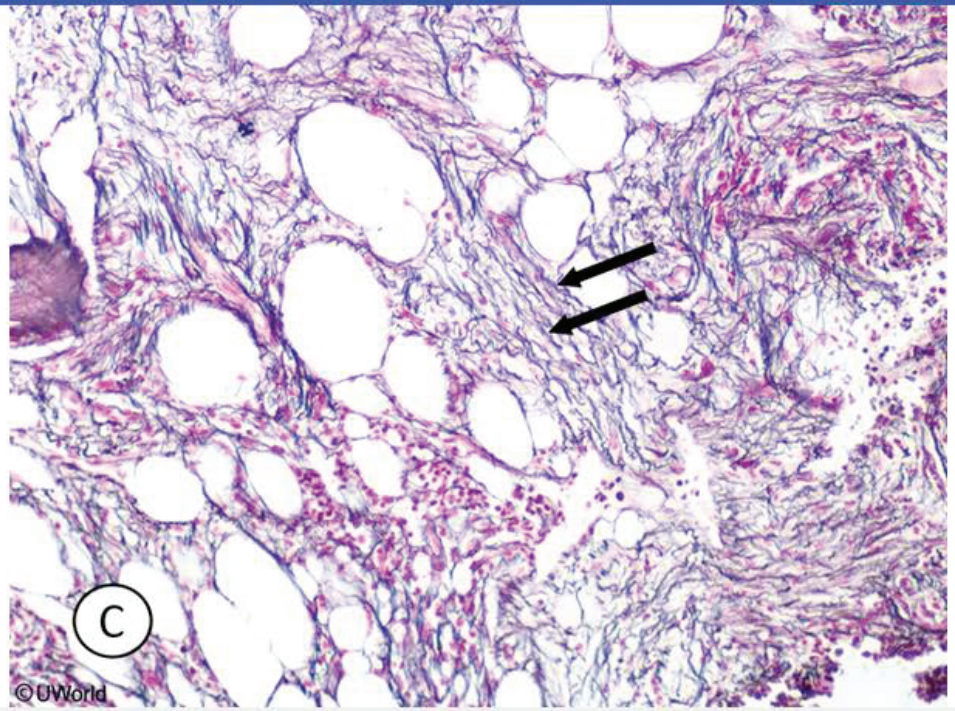
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This patient wit… has **primary m… **megakaryocy… which stimulate… **marrow fibros…

- **Extramed…** hematopo… results in …
- **Cytopenia** Therefore…
- **Dacrocyte** the fibrotic… teardrop-s…

The diagnosis … frequently resu… marrow biopsy… atypical megak…

Exhibit Display



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atypical megakaryocytes confirms the diagnosis.

(Choice B) Multiple myeloma, a clonal disorder of plasma cells, is marked by a monoclonal spike (M-spike) on protein electrophoresis. Patients typically have anemia, hypercalcemia, bone pain (osteolytic lesions), and renal insufficiency. Bone marrow biopsy usually shows a hypercellular marrow with monoclonal clusters of plasma cells.

(Choice C) Anemia of chronic disease is associated with hepcidin-induced changes in iron metabolism that cause iron trapping within macrophages. Bone marrow biopsy with Prussian blue stain demonstrates increased iron within macrophages. Hepatosplenomegaly and teardrop cells would be unexpected.

(Choice D) Myelodysplasia is a malignant stem cell cancer associated with the production of dysplastic, atypical blood cells. Although most patients with myelodysplasia have cytopenias, the bone marrow is usually hypercellular with multi-lineage dysplasia.

(Choice E) Aplastic anemia results from injury (eg, drugs, radiation, viruses) to multipotent hematologic stem cells. It is usually associated with pancytopenia and a profoundly hypocellular bone marrow that is infiltrated with adipose. However, extracellular hematopoiesis is minimal and hepatosplenomegaly and dacrocytes are not typically present.

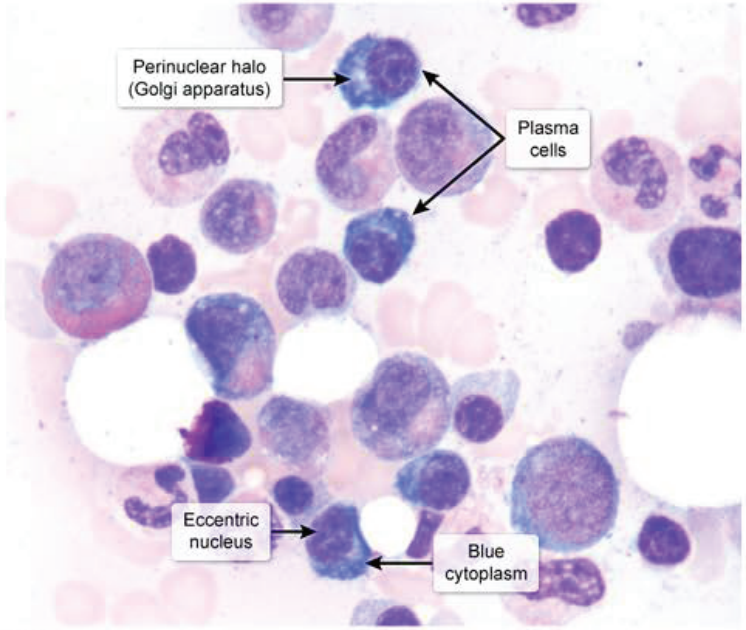
Educational objective:

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Exhibit Display

Multiple myeloma



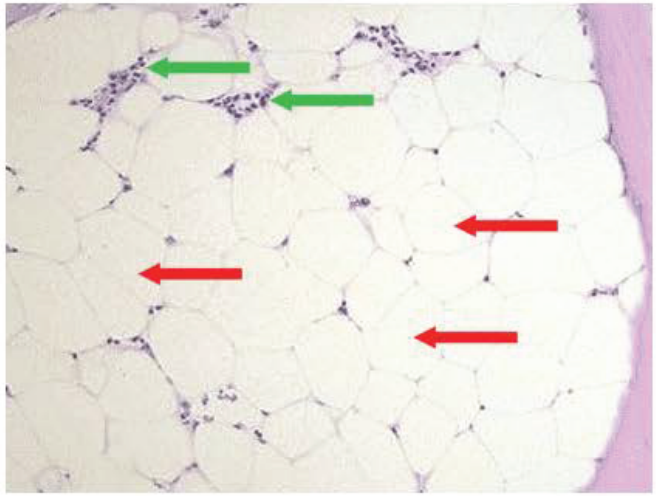
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Educational objective:

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Educational objective:

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(Choice D) Myelodysplasia is a malignant stem cell cancer associated with the production of dysplastic, atypical blood cells. Although most patients with myelodysplasia have cytopenias, the bone marrow is usually hypercellular with multi-lineage dysplasia.

(Choice E) Aplastic anemia results from injury (eg, drugs, radiation, viruses) to multipotent hematologic stem cells. It is usually associated with pancytopenia and a profoundly hypocellular bone marrow that is infiltrated with adipose. However, extracellular hematopoiesis is minimal and hepatosplenomegaly and dacrocytes are not typically present.

Educational objective:
Primary myelofibrosis is a myeloproliferative disorder associated with the clonal expansion of megakaryocytes. Bone marrow fibrosis accounts for most of the major manifestations, including hepatosplenomegaly, cytopenias, and blood smear evidence of dacrocytes. Bone marrow aspiration is usually dry, but bone marrow biopsy will show marked fibrosis with occasional clusters of atypical megakaryocytes.

Pathology	Hematology & Oncology	Myelofibrosis
Subject	System	Topic

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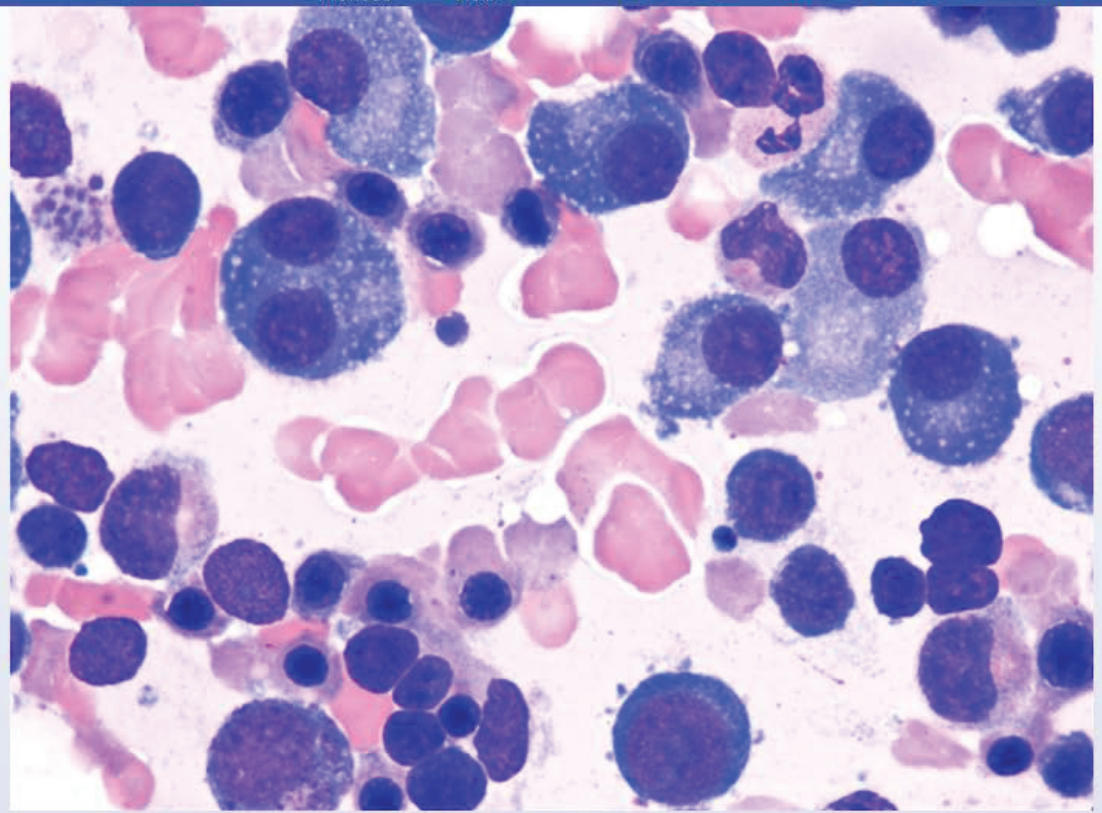
A 59-year-old man comes to the office due to 3 months of progressive fatigue and back pain. The back pain occurs mainly with movement or positional changes. Physical examination reveals midline tenderness over the middle and lower back. Laboratory evaluation shows a hemoglobin level of 10.2 g/dL and serum calcium level of 12 mg/dL. A bone marrow aspirate is performed, and the histopathologic findings are shown below.

This patient is at greatest risk for developing which of the following conditions?

A. Amyloidosis
B. Cardiac tamponade
C. Hepatic failure
D. Hyperthyroidism
E. Meningeal carcinomatosis
F. Splenic rupture

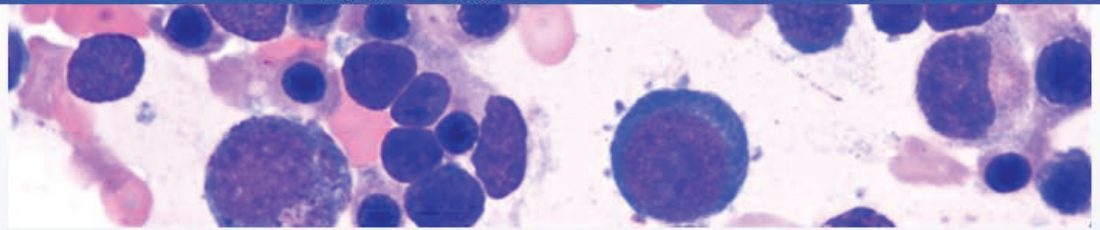
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This patient is at greatest risk for developing which of the following conditions?

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This patient is at greatest risk for developing which of the following conditions?

- A. Amyloidosis (72%)
- B. Cardiac tamponade (2%)
- C. Hepatic failure (4%)
- D. Hyperthyroidism (1%)
- E. Meningeal carcinomatosis (3%)
- F. Splenic rupture (15%)

Correct

72%

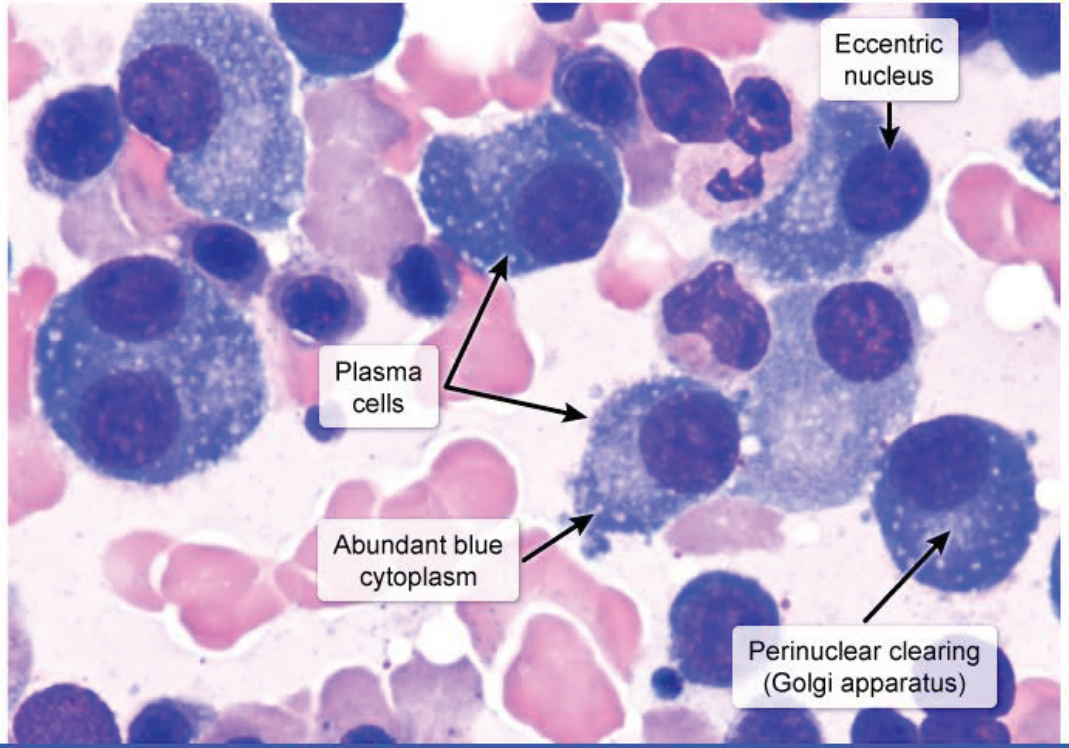
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Plasma cells



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This patient's bone marrow aspirate shows **numerous plasma cells**, which can be identified by abundant basophilic cytoplasm, eccentric nuclei, well-developed Golgi apparatus (perinuclear paleness), and "clock-face" (peripheral) chromatin. A bone marrow sample with >10% plasma cells is strongly suggestive of **multiple myeloma** (MM), a clonal plasma cell malignancy.

In MM, neoplastic plasma cells:

- Replicate in the bone marrow and choke out normal hematopoiesis, leading to **normocytic, normochromic anemia** (impaired erythropoiesis) and increased risk of infection (impaired B-cell lymphopoiesis).
- Secrete osteolytic cytokines, leading to bone pain, osteolytic (radiolucent) bone lesions, and **hypercalcemia**.
- Produce large quantities of **monoclonal immunoglobulin** (paraprotein) composed of heavy and light chains (eg, IgG, IgA) or light chains alone. Light chains can deposit in the renal tubules, leading to **light-chain cast nephropathy**, which is usually characterized by mild renal insufficiency and waxy, laminated urinary casts (Bence Jones).
- Light chains can also form **insoluble fibrils** and deposit in major organs, leading to **amyloid light-**

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- Light chains can also form **insoluble fibrils** and deposit in major organs, leading to **amyloid light-chain amyloidosis**. This can contribute to the already elevated risk of renal failure as well as heart failure and neurologic dysfunction. Amyloidosis can often be identified on biopsy using hematoxylin and eosin stain (eosinophilic extracellular deposits) or Congo red stain viewed under polarized light (apple-green birefringence).

(Choice B) Cardiac tamponade can be associated with some neoplasms (eg, lung, breast) due to tumor invasion of the pericardium. MM does not typically cause pericardial disease; therefore, it is not associated with cardiac tamponade.

(Choice C) Hepatic failure is most often linked to viral hepatitis or alcohol abuse. It occasionally occurs due to malignant infiltration of the liver (eg, lymphoma, breast cancer); however, risk of hepatic failure with MM is low; amyloidosis is a far more common complication.

(Choice D) Hyperthyroidism is most often due to Graves disease, an autoimmune disorder that generates TSH-receptor antibodies. It can also be seen with medications (eg, lithium) and tumors that produce TSH (eg, pituitary adenoma). MM is not linked to hyperthyroidism.

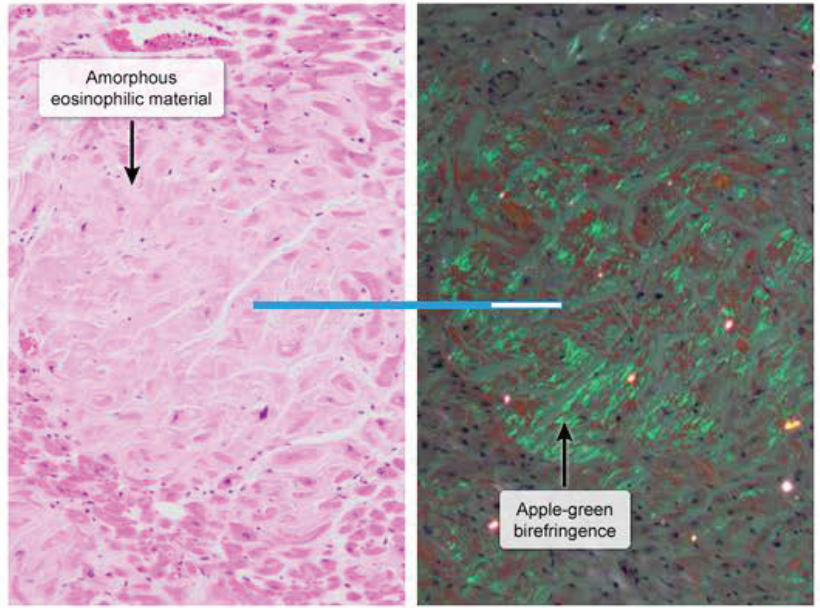
(Choice E) Meningeal carcinomatosis is a rare condition associated with some solid tumors (eg, breast cancer, lung cancer, melanoma). Tumor spread to the leptomeninges can cause mass effect (eg,

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Exhibit Display

Amyloid



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H&E stain

Congo red stain under polarized light

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(eg, pituitary adenoma). MM is not linked to hyperthyroidism.

(Choice E) Meningeal carcinomatosis is a rare condition associated with some solid tumors (eg, breast cancer, lung cancer, melanoma). Tumor spread to the leptomeninges can cause mass effect (eg, headache, hydrocephalus), cranial/spinal nerve dysfunction, and focal neurologic issues. MM does not typically spread to the leptomeninges.

(Choice F) Atraumatic splenic rupture can occur with leukemia and lymphoma due to massive splenomegaly from extramedullary hematopoiesis and/or underlying tumor infiltration. MM does not typically cause significant extramedullary hematopoiesis and usually replicates in the bone marrow, not the spleen.

Educational objective:
Amyloid light-chain amyloidosis is associated with multiple myeloma and other monoclonal plasma cell dyscrasias due to the deposition of insoluble immunoglobulin light-chain fibrils in major organs (eg, kidneys, heart, neurologic system). A bone marrow sample with >10% plasma cells is strongly suggestive of multiple myeloma.

Pathology	Hematology & Oncology	Multiple myeloma
Subject	System	Topic

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A 30-year-old man with a history of intravenous drug abuse and known HIV infection comes to the emergency department because of increasing abdominal distention and anorexia. A CT scan of the abdomen shows ascites and a large mass surrounding the small intestine. Biopsy of the mass reveals uniform, round, medium-sized tumor cells with basophilic cytoplasm and a proliferation fraction (Ki-67 fraction) of > 99%. Which of the following infectious agents is most closely associated with the development of his current condition?

A. Epstein-Barr virus
B. Human papillomavirus serotype 31 or 33
C. *Helicobacter pylori*
D. Human herpesvirus 8
E. Hepatitis B

Submit

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- C. *Helicobacter pylori*
- D. Human herpesvirus 8
- E. Hepatitis B

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✓ A. Epstein-Barr virus (45%)

B. Human papillomavirus serotype 31 or 33 (3%)

C. *Helicobacter pylori* (12%)

✗ D. Human herpesvirus 8 (21%)

E. Hepatitis B (17%)

Incorrect
Correct answer
A

45%
Answered correctly

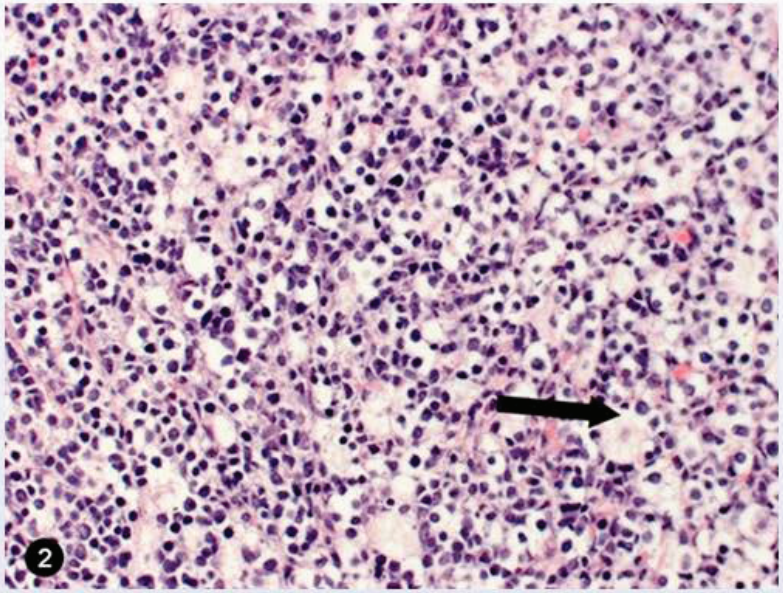
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Time Spent

10/16/2020
Last Updated

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Explanation



Epstein-Barr virus (EBV) is the etiologic agent most strongly associated with Burkitt lymphoma, with infection being present in 40% of immunodeficiency-associated Burkitt lymphoma and nearly all cases of endemic Burkitt lymphoma. A crucial step in the transformation of infected cells is the balanced t(8;14)

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Epstein-Barr virus (EBV) is the etiologic agent most strongly associated with Burkitt lymphoma, with infection being present in 40% of immunodeficiency-associated Burkitt lymphoma and nearly all cases of endemic Burkitt lymphoma. A crucial step in the transformation of infected cells is the balanced t(8;14) translocation, which causes overexpression of c-MYC, a transcriptional regulator that controls cell proliferation. Chronic EBV infection increases B-cell proliferation and is thought to increase the risk of a c-MYC translocation. Pre-existing immunodeficiency secondary to HIV infection can potentiate EBV antigen-induced B-cell proliferation. The histology described is classic for Burkitt lymphoma: diffuse medium-sized lymphocytes and a high proliferation index represented by the high Ki-67 fraction (approaching 100%). The classic "starry sky" appearance is usually seen, and is due to the presence of benign macrophages.

(Choice B) Human papillomavirus (HPV) types 31, 33, 35, and 51 have been identified in invasive squamous cancers of the cervix, although HPV 16 and 18 are most commonly associated. The viral DNA is usually integrated into the hostcell genome.

(Choice C) Although *H. pylori* infection may play a role in the development of gastrointestinal lymphomas, it more commonly causes chronic gastritis and peptic ulcer disease. Lymphomas associated with *H. pylori*

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is usually integrated into the hostcell genome.

(Choice C) Although *H. pylori* infection may play a role in the development of gastrointestinal lymphomas, it more commonly causes chronic gastritis and peptic ulcer disease. Lymphomas associated with *H. pylori* infection would be expected to have a different type and histology (usually MALT lymphomas).

(Choice D) Human herpesvirus 8 infection can cause Kaposi's sarcoma and primary effusion lymphoma (arising from B-cells), most commonly in HIV infected patients. The histology of primary effusion lymphoma is distinct from Burkitt lymphoma, with large cells, big nuclei, and prominent nucleoli.

(Choice E) Hepatitis B infection can cause hepatocellular carcinoma. A CT scan would reveal the presence of a tumor mass or masses within the liver. Hepatocellular carcinoma, being derived from hepatocytes, is histologically and cytologically distinct from B-cell lymphomas.

Educational objective:

The Epstein-Barr virus genome is identified in approximately 50% of systemic B-cell lymphomas and almost all primary CNS lymphomas occurring in the setting of HIV infection. A high mitotic index is typical of Burkitt lymphoma.

Pathology Hematology & Oncology Burkitt lymphoma

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A 22-year-old woman comes to the emergency department due to a nosebleed. She had a similar episode yesterday, but the bleeding stopped with prolonged local pressure. On review of systems, the patient has also had easy bruising for the past several months. She has no significant past medical history and takes no medications. On physical examination, her heart and lungs appear normal. The liver span is 8 cm and the spleen is not palpable. There are scattered ecchymoses over her arms and legs. Laboratory results are as follows:

Hematocrit	45%
Platelet count	9,000/mm^3
Leukocytes	5,500/mm^3
Neutrophils	60%
Eosinophils	2%
Lymphocytes	32%
Monocytes	6%
	250 mg/dL (normal:

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Lymphocytes	32%
Monocytes	6%
Fibrinogen	250 mg/dL (normal: 150-350 mg/dL)
Prothrombin time	13 sec

HIV and hepatitis C tests are negative. Which of the following is the most likely primary mechanism causing this patient's condition?

A. Bone marrow aplasia
B. Bone marrow infiltration by malignant cells
C. Disseminated intravascular coagulation
D. Immune destruction of platelets
E. Platelet sequestration
F. von Willebrand disease

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150-350 mg/dL)

Prothrombin time	13 sec

HIV and hepatitis C tests are negative. Which of the following is the most likely primary mechanism causing this patient's condition?

A. ~~Bone marrow aplasia~~ (1%)
B. ~~Bone marrow infiltration by malignant cells~~ (2%)
C. ~~Disseminated intravascular coagulation~~ (3%)
✓ D. Immune destruction of platelets (71%)
E. ~~Platelet sequestration~~ (6%)
✗ F. von Willebrand disease (14%)

Incorrect
Correct answer

71%
Answered correctly

01 min, 09 secs
Time Spent

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This patient has recurrent epistaxis, ecchymoses, and marked thrombocytopenia (normal 150,000-400,000/mm^3). She has a normal hematocrit, leukocyte count and differential, fibrinogen level, and prothrombin time/International Normalized Ratio. She takes no medications, and there is no obvious hepatosplenomegaly on physical examination. Taken together, these findings suggest an isolated acquired thrombocytopenia.

Common causes of acquired thrombocytopenia include increased platelet consumption, sequestration, and/or destruction. In this patient, primary **immune thrombocytopenic purpura (ITP)** is the most likely diagnosis as, other than thrombocytopenia (with associated ecchymosis), her physical examination and laboratory findings are unremarkable. ITP is characterized by the **autoimmune** destruction of platelets by anti-platelet antibodies, likely IgG autoantibodies against the platelet membrane glycoproteins GPIIb/IIIa. In children, ITP is typically acute and self-limited, whereas it tends to run an insidious and chronic course in adults. A peripheral blood smear with **isolated** thrombocytopenia and no other platelet abnormalities would help confirm the diagnosis (megakaryocytes can sometimes be seen). Treatment involves systemic immunosuppression (corticosteroids). Secondary ITP is sometimes associated with HIV or hepatitis C infection.

(Choice A) Bone marrow aplasia would cause pancytopenia. It is unlikely that this patient's

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(Choice A) Bone marrow aplasia would cause pancytopenia. It is unlikely that this patient's thrombocytopenia is due to bone marrow failure as the peripheral counts of the hematopoietic cell lines, other than platelets, are normal. Common causes of aplastic anemia include parvovirus and Epstein-Barr virus infections, high-dose chemotherapy, and radiation.

(Choice B) Malignant infiltration of the bone marrow would be expected to cause pancytopenia and extramedullary hematopoiesis within the liver and spleen, leading to hepatosplenomegaly.

(Choice C) If this patient were experiencing accelerated platelet consumption due to disseminated intravascular coagulation, the plasma fibrinogen level would be decreased and the prothrombin time would be elevated due to clotting factor consumption.

(Choice E) Splenic sequestration of platelets typically occurs in disorders that produce splenomegaly, such as portal hypertension; the platelet count usually remains >30,000/mm^3, and abnormal bleeding generally does not occur. Although platelets can undergo splenic sequestration in ITP, the primary mechanism responsible for the thrombocytopenia is immune destruction.

(Choice F) In von Willebrand disease, platelet function is impaired because von Willebrand factor, which normally facilitates platelet binding to damaged endothelium, is deficient. The platelet count would be normal (unlike in this patient), and the bleeding time and partial thromboplastin time would be prolonged.

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(Choice F) In von Willebrand disease, platelet function is impaired because von Willebrand factor, which normally facilitates platelet binding to damaged endothelium, is deficient. The platelet count would be normal (unlike in this patient), and the bleeding time and partial thromboplastin time would be prolonged.

Educational objective:
Autoimmune platelet destruction is a common cause of thrombocytopenia and should be suspected in patients with ecchymoses, petechiae, mucosal bleeding, and no other obvious causes of thrombocytopenia (eg, medications, bone marrow failure).

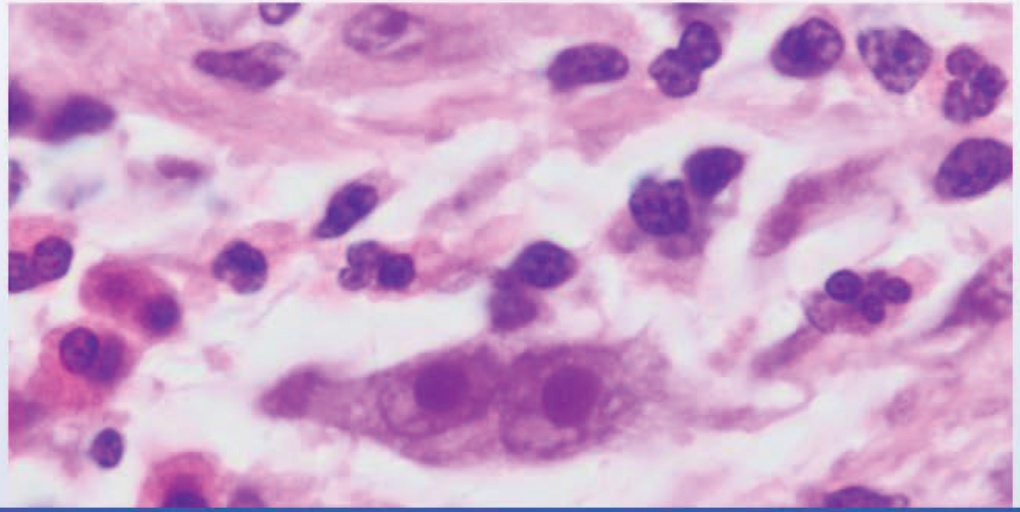
Pathology	Hematology & Oncology	ITP
Subject	System	Topic

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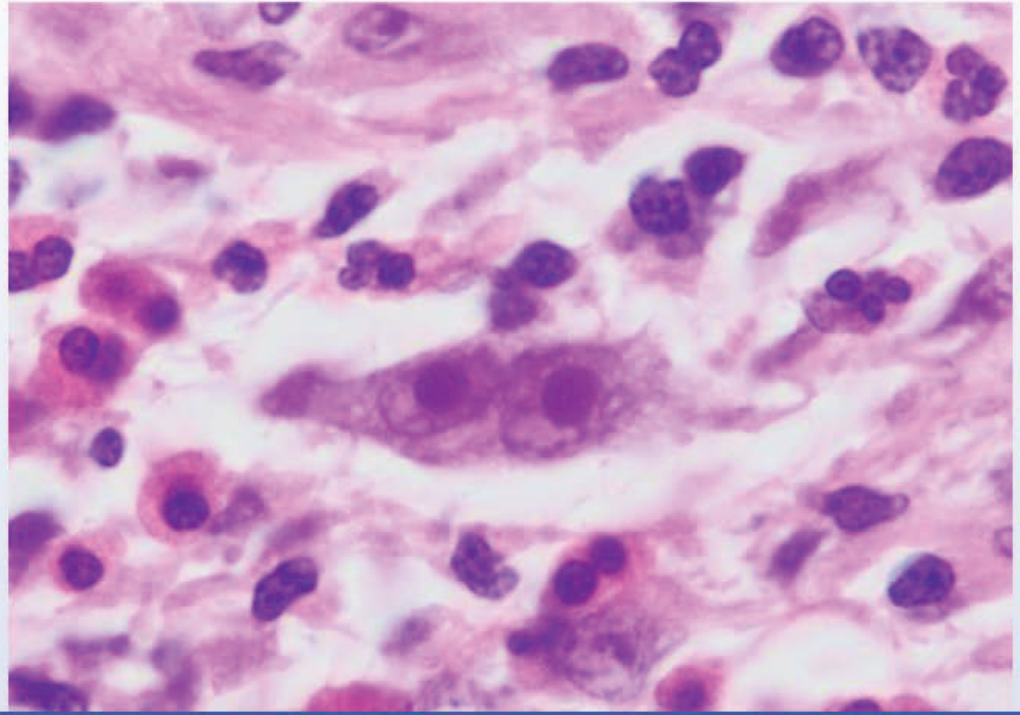
A 28-year-old previously healthy man comes to the office due to episodic fevers, night sweats, and weight loss for several months. He emigrated from Kenya with his family at age 14. He does not use tobacco, alcohol, or illicit drugs. The patient works as a driving instructor and volunteers at a homeless shelter. His temperature is 37.2 C (99 F). Physical examination is normal with the exception of cervical lymphadenopathy. A lymph node biopsy is performed, and histopathologic findings are shown in the image below.



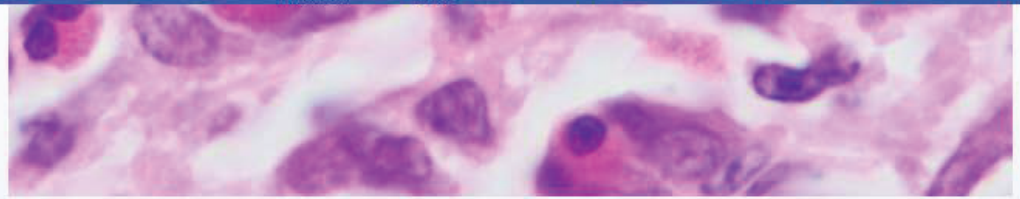
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temperature is 37.2 C (99 F). Physical examination is normal with the exception of cervical lymphadenopathy. A lymph node biopsy is performed, and histopathologic findings are shown in the image below.



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Which of the following is the most likely diagnosis?

- A. Burkitt lymphoma (13%)
- B. Follicular lymphoma (1%)
- ✓ C. Hodgkin lymphoma (81%)
- D. Large B-cell lymphoma (2%)
- E. Multiple myeloma (0%)
- F. Tuberculosis (0%)

Correct

81% Answered correctly

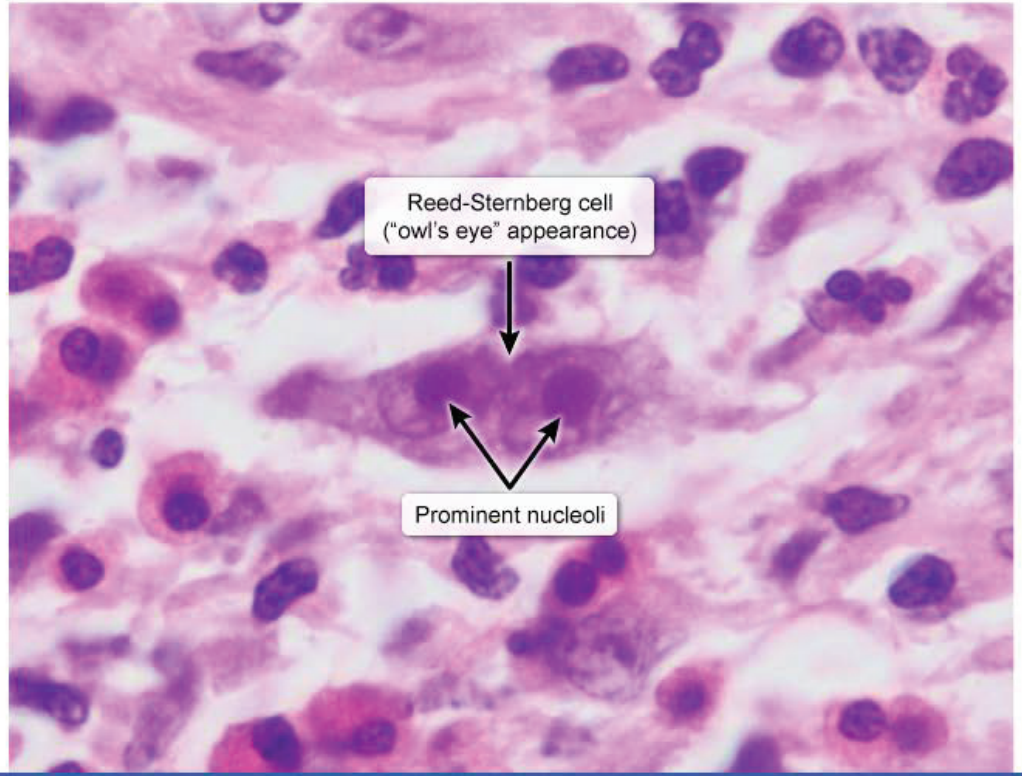
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Hodgkin lymphoma



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This patient most likely has classic **Hodgkin lymphoma (HL)**. The typical presentation is either nontender **lymphadenopathy** or lymphadenopathy incidentally detected on routine chest x-ray. Many patients develop associated systemic **B symptoms** (fevers, night sweats, weight loss). HL has a **bimodal age distribution** with a peak in the 20s (or younger in some countries) and another in the 60s. The complete blood count and peripheral blood smear are usually unremarkable.

A **lymph node biopsy** can distinguish HL from benign causes of lymphadenopathy. The key to diagnosing classic HL is detecting the characteristic **Reed-Sternberg** (RS) cell on hematoxylin and eosin preparation. RS cells have ample cytoplasm, a multilobed nucleus or multiple nuclei, and inclusion-like nucleoli. RS cells are seen against a background of lymphocytes, histiocytes, and eosinophils in classic HL.

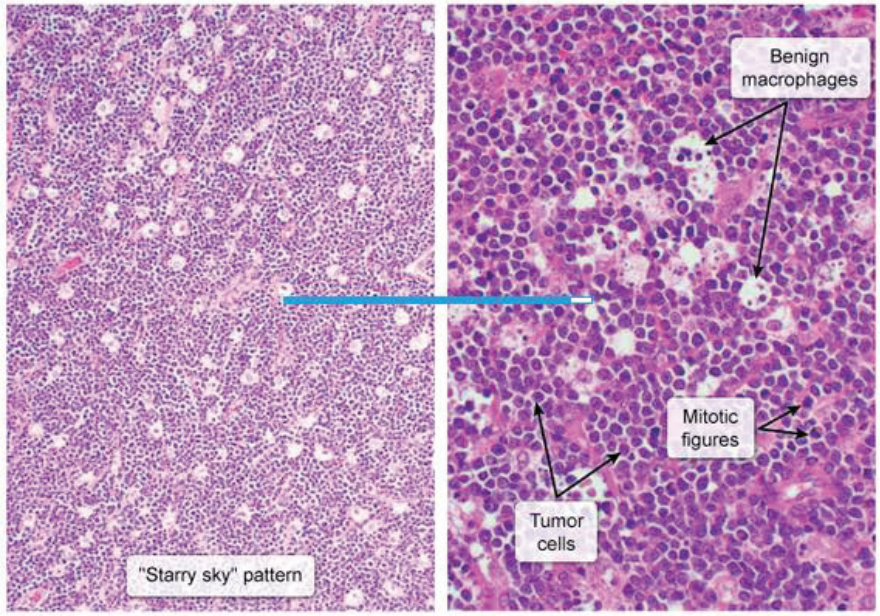
(Choice A) Burkitt lymphoma often presents as a mass in the abdomen/pelvis (or the jaw in the endemic [African] form, which has a peak incidence in boys around age 5). However, histology would show a monotonous population of medium-sized lymphoid cells with many tingible body macrophages, giving a "starry sky" appearance. High numbers of mitotic cells and apoptotic bodies would be seen.

(Choice B) Follicular lymphoma shows aggregates of closely packed, neoplastic lymph node follicles. Two major cell types, centrocytes (small cleaved cells) and centroblasts (large noncleaved cells), are

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Exhibit Display

Burkitt lymphoma



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Two major cell types, centrocytes (small cleaved cells) and centroblasts (large noncleaved cells), are

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Two major cell types, centrocytes (small cleaved cells) and centroblasts (large noncleaved cells), are observed. Older adults tend to be affected. Waxing and waning painless lymphadenopathy (typically without B symptoms) is common.

(Choice D) Large B-cell lymphoma is characterized by diffuse sheets of large, atypical lymphoid cells with nuclei at least 5 times the size of small lymphocytes. RS cells against a background of mixed inflammation is not a characteristic histologic feature of large B-cell lymphoma.

(Choice E) Multiple myeloma, a plasma cell dyscrasia characterized by proliferation of clonal plasma cells, is predominantly a disease of the elderly. It is characterized by osteolytic lesions, although spread to nodal and extranodal sites can occur.

(Choice F) Tuberculosis is on the differential diagnosis for this patient, who is from Kenya, volunteers at homeless shelters, and has had night sweats and weight loss. However, histology in tuberculosis would show caseating granulomas, not RS cells.

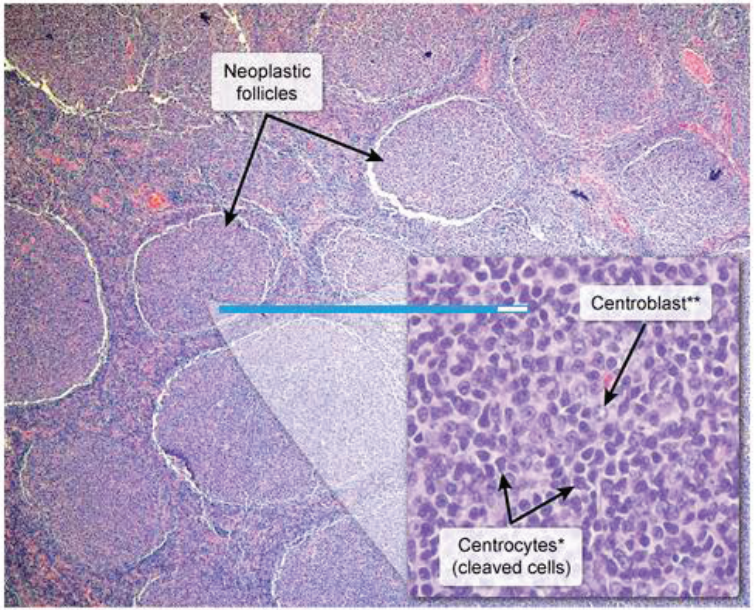
Educational objective:
The presence of Reed-Sternberg (RS) cells on lymph node biopsy is a diagnostic feature of classic Hodgkin lymphoma. RS cells have abundant cytoplasm, a multilobed nucleus or multiple nuclei, and inclusion-like nucleoli.

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"starry sky" appearance. High numbers of mitotic cells and apoptotic bodies would be seen.

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Follicular lymphoma

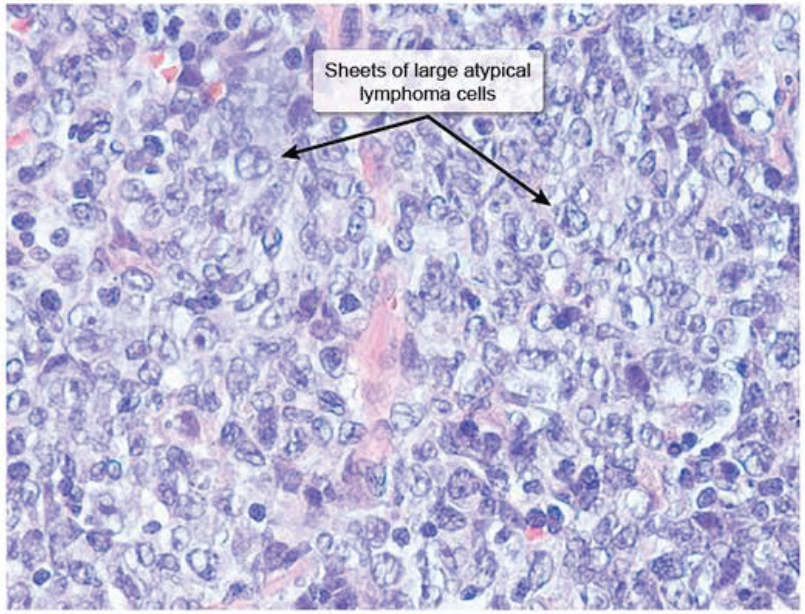


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"starry sky" appearance. High numbers of mitotic cells and apoptotic bodies would be seen.

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Diffuse large B-cell lymphoma*



*Most common type of non-Hodgkin lymphoma.

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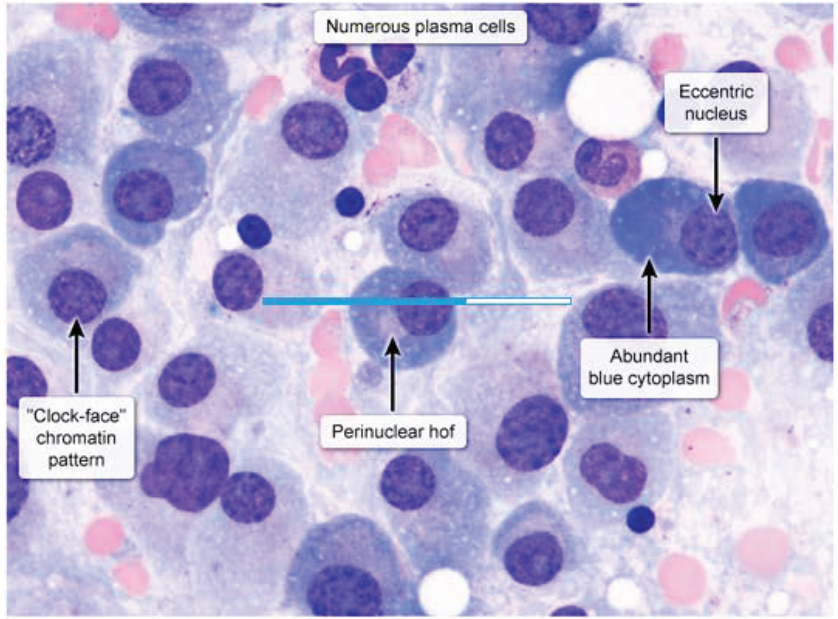
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"starry sky" appearance. High numbers of mitotic cells and apoptotic bodies would be seen.

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Multiple myeloma

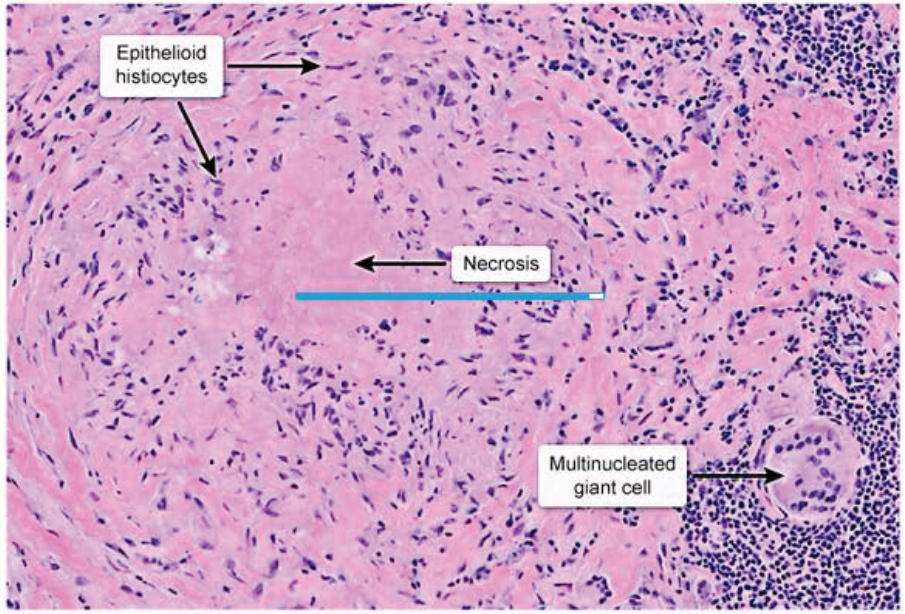


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"starry sky" appearance. High numbers of mitotic cells and apoptotic bodies would be seen.

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Caseating granuloma



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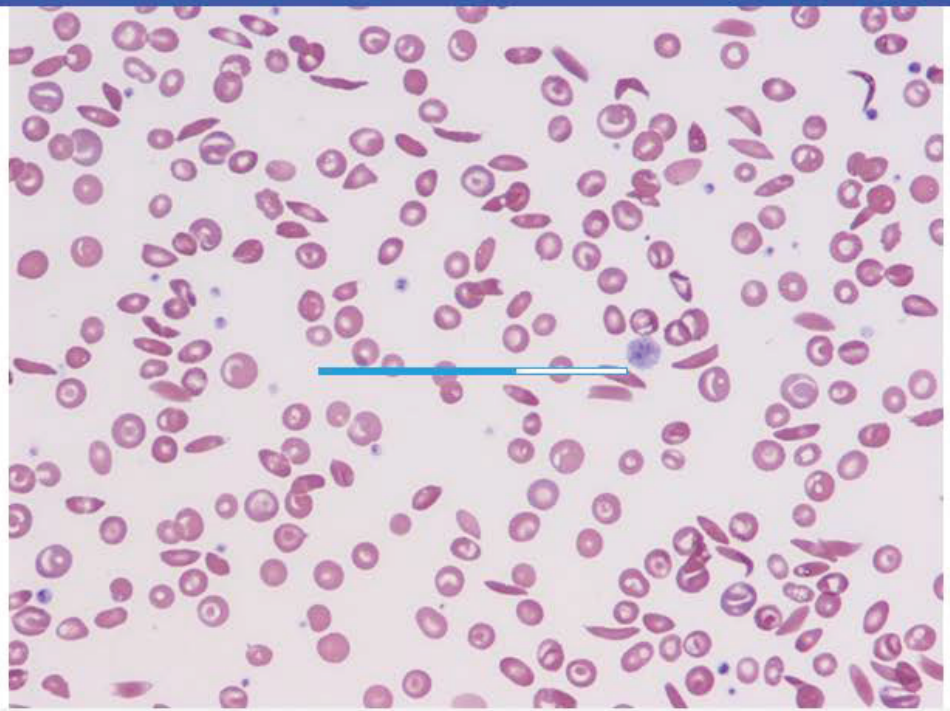
An 8-year-old boy is brought to the emergency department due to 24 hours of fever and chills. Temperature is 38.3 C (101 F). On examination, the patient is lethargic with dry mucous membranes. There are no oropharyngeal lesions, and tympanic membranes are normal. The lungs are clear on auscultation, and heart sounds are normal. The abdomen is soft and nontender. There is no skin rash. Laboratory testing shows a leukocyte count of 24,000/mm^3 with 15% bands, 80% neutrophils, and 5% lymphocytes. Peripheral blood smear is shown in the exhibit. Blood cultures are obtained and intravenous fluids and empiric antibiotics are initiated. The patient's blood cultures are most likely to grow which of the following organisms?

A. *Escherichia coli* (22%)
B. *Pseudomonas aeruginosa* (8%)
C. *Staphylococcus aureus* (11%)
✓ D. *Streptococcus pneumoniae* (47%)
E. *Streptococcus pyogenes* (5%)
F. Viridans streptococci (3%)

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Patients with **sickle cell anemia** have mutations in the beta-globulin gene that cause hemoglobin to reversibly polymerize when deoxygenated, which leads to the formation of sickled-shaped erythrocytes that clog small capillaries and cause end-organ ischemia. The spleen is particularly vulnerable; repeated microinfarction of splenic vascular beds usually results in **functional asplenia** within the first 18-36 months of life.

Because the spleen produces opsonizing antibodies that are important for clearing **encapsulated bacteria** from the blood, asplenia is associated with significant risk of fulminant bacterial infections. ***Streptococcus pneumoniae*** is the leading pathogen, but *Neisseria meningitidis* and *Haemophilus influenzae* are also frequently isolated. Therefore, patients with sickle cell anemia who present with signs/symptoms of infection (eg, fever, chills, leukocytosis) require urgent empiric antibiotic therapy that covers these pathogens. Vaccination (pneumococcal and *Haemophilus influenzae* type b) is recommended to reduce risk of future infection.

(Choices A, B, C, E, and F) Patients with sickle cell anemia are at increased risk for overwhelming bacterial infections with a variety of pathogens. However, *S pneumoniae* infections are particularly common, accounting for 40%-60% of total bacterial infections in this population. Although *Pseudomonas*

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infection (eg, fever, chills, leukocytosis) require urgent empiric antibiotic therapy that covers these pathogens. Vaccination (pneumococcal and *Haemophilus influenzae* type b) is recommended to reduce risk of future infection.

(Choices A, B, C, E, and F) Patients with sickle cell anemia are at increased risk for overwhelming bacterial infections with a variety of pathogens. However, *S pneumoniae* infections are particularly common, accounting for 40%-60% of total bacterial infections in this population. Although *Pseudomonas aeruginosa* is encapsulated, it is not a common pathogen in patients with sickle cell disease (it occurs more often in those with cystic fibrosis, severe chronic obstructive pulmonary disease, and diabetes mellitus). Patients with sickle cell anemia are also particularly prone to salmonella osteomyelitis.

Educational objective:
Patients with sickle cell disease become functionally asplenic within the first few years of life due to repeated microinfarction of splenic vascular beds. This dramatically increases the risk for fulminant infections with encapsulated bacterial organisms, particularly *Streptococcus pneumoniae*. Patients with sickle cell disease are also at increased risk for other bacterial infections, most notably salmonella osteomyelitis.

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A 24-year-old African American woman comes to the office with her husband for prenatal counseling. She has a 3-year-old child with sickle cell anemia from a previous marriage, and the child's father died in a car accident. The patient remarried last year and is interested in having more children. She and her new husband do not have sickle cell anemia, and the patient's husband has no other children. However, the patient and her husband are worried that their future children could have sickle cell anemia. A urine pregnancy test is negative. Which of the following is the best initial test that can be offered to this couple?

A. ~~Chorionic villous sampling during future pregnancy~~ (2%)

B. ~~Maternal hemoglobin electrophoresis~~ (19%)

C. Northern blot analysis of paternal blood sample (5%)

D. Paternal hemoglobin electrophoresis (68%)

E. Paternal karyotype analysis (3%)

Correct

68% Answered correctly

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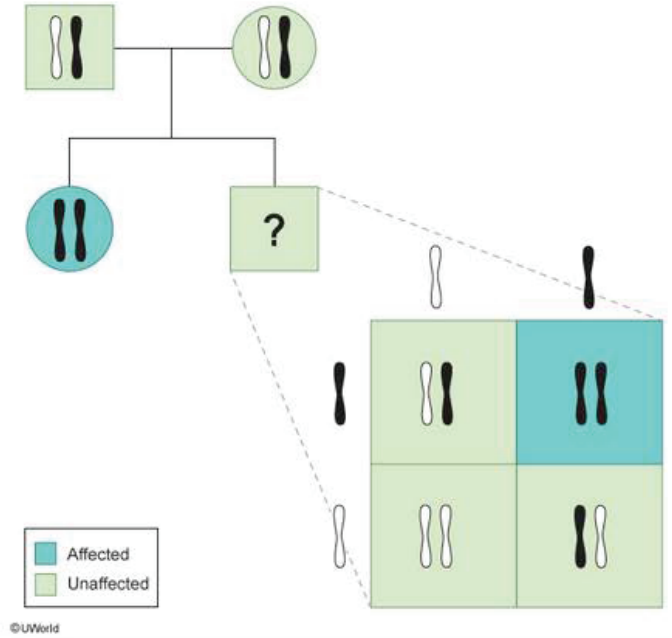
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Transmission of autosomal recessive disorder



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Sickle cell anemia is an **autosomal recessive** hemoglobinopathy. Affected patients must inherit 2 mutant genes for hemoglobin S (HbS), one from each parent. In order for an offspring of 2 parents without sickle cell anemia to be affected, **both parents must carry the sickle cell trait**. Any offspring resulting from such pairings will have a 1 in 4 chance of having sickle cell disease (SCD). This patient is a carrier of the sickle cell trait as she has a child with sickle cell anemia.

Hemoglobin electrophoresis, a type of gel electrophoresis, is used to determine if the patient's new husband also has sickle cell trait. Abnormal hemoglobin (eg, HbS), moves at a slower speed than normal hemoglobin due to the replacement of glutamic acid by valine. The husband's test results combined with the maternal family history will determine the risk that future offspring will inherit sickle cell anemia.

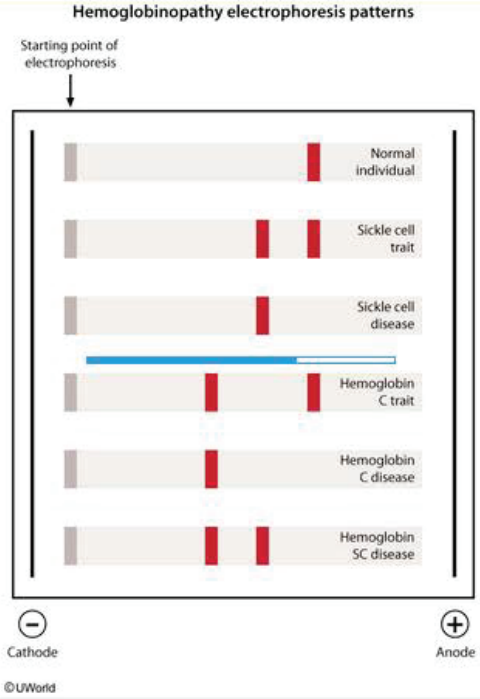
(Choice A) The chorionic villi are part of the placenta and, as such, are fetal tissue. Once fetal DNA is obtained, DNA sequencing can be performed to evaluate for sickle cell mutation. Chorionic villus sampling (CVS) can be performed at 10-14 weeks gestation. However, it is relatively invasive and carries a risk of miscarriage, spotting/bleeding, infection, and other complications. CVS is not helpful to a patient who wishes to determine her risk prior to conception.

(Choice B) It is not necessary to perform maternal hemoglobin electrophoresis as it has been established

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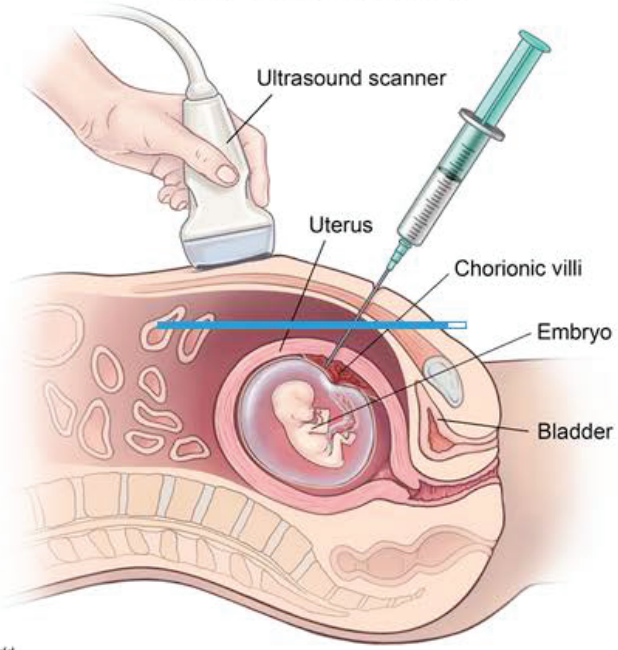
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Exhibit Display

Chorionic villus sampling



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wishes to determine her risk prior to conception.

(Choice B) It is not necessary to perform maternal hemoglobin electrophoresis as it has been established from this patient's history that she has sickle cell trait.

(Choice C) Northern blots use electrophoresis to separate RNA by size, followed by the application of a DNA probe to detect a specific RNA molecule. This allows for the quantification of the RNA expression of specific genes. Hemoglobin electrophoresis is a more appropriate test for SCD as it involves the separation of protein (eg, hemoglobin) rather than RNA.

(Choice E) A karyotype is a visual analysis of all the chromosomes in a cell ordered by size and stained to reveal chromosomal banding. SCD results from a single nucleotide mutation, not from any abnormality in overall chromosome structure. Disorders due to chromosomal abnormalities include Klinefelter syndrome (47,XXY), Turner syndrome (45,XO) and trisomy disorders.

Educational objective:
Sickle cell anemia is an autosomal recessive hemoglobinopathy. In order for a child to have sickle cell disease, both parents must be carriers. Hemoglobin electrophoresis can be used to determine the carrier status of a prospective parent who has no history of sickle cell anemia.

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A 7-year-old boy is admitted to the hospital after his adoptive parents brought him to the emergency department due to fatigue and pallor. Laboratory evaluation reveals pancytopenia with an absolute neutrophil count consistent with severe neutropenia. Bone marrow examination reveals signs of aplastic anemia, and subsequent genetic testing reveals a congenital genomic defect in DNA repair leading to chromosomal instability. A bone marrow transplant is required for treatment. The patient's only living relatives are an identical twin brother and older sister who were both adopted by the same parents. He also has stored umbilical stem cells that were harvested after birth. Which of the following is the best bone marrow transplantation method for this patient?

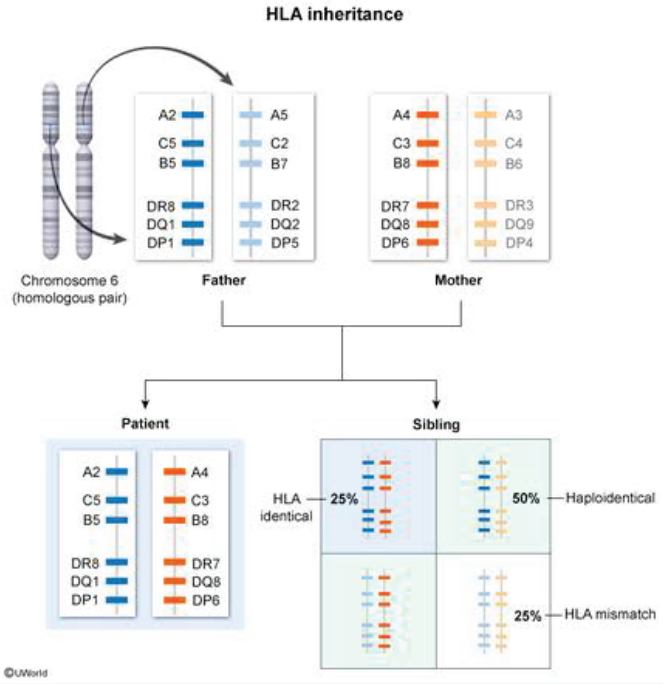
A. ~~Freshly harvested autologous transplant~~ (3%)
B. Matched unrelated donor (34%)
C. ~~Stored umbilical cord stem cells from the patient~~ (25%)
D. Twin sibling syngenetic transplant (29%)
E. Unmatched sibling allogeneic transplant (6%)

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Explanation

Exhibit Display



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Hematologic stem cell transplantation (HCT) requires identification of a donor with similar **human leukocyte antigens** (HLAs), polymorphic proteins expressed on the surface of every cell. The most important HLA proteins to match are **HLA-A, B, and C**, which form major histocompatibility complex class I molecules, and **HLA-DP, DQ, and DR**, which form major histocompatibility complex class II molecules. Because these HLAs play a vital role in the differentiation between self and nonself, recipients who receive well-matched donor cells have lower rates of graft rejection (ie, host cells attack the donor) and graft-versus-host disease (ie, donor cells attack the host).

Donor sources are generally categorized as follows:

- **Autologous**: Stem cells harvested from the patient or banked from the patient's cord blood at birth are transplanted to reconstitute the patient's bone marrow. However, autologous transplants cannot be used for congenital genetic disorders because the genetic mutation will be present in all cells harvested from the patient **(Choices A and C)**.
- **Syngenetic**: Identical twins have the same genome; therefore, cells transplanted from one identical twin to the other will be an exact HLA match and will not cause graft rejection or graft-versus-host disease. However, syngenetic transplants are not helpful for congenital genetic conditions because any congenital mutation present in one twin will be present in the other **(Choice D)**

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harvested from the patient **(Choices A and C)**.

- **Syngenetic**: Identical twins have the same genome; therefore, cells transplanted from one identical twin to the other will be an exact HLA match and will not cause graft rejection or graft-versus-host disease. However, syngenetic transplants are not helpful for congenital genetic conditions because any congenital mutation present in one twin will be present in the other **(Choice D)**.
- **Allogeneic donors**: Donors who do not have the same genome as the patient are classified as related or unrelated.
  - **Related donors**: Because HLA alleles are encoded on chromosome 6, each nonidentical sibling has a 25% chance of being an exact HLA match (HLA identical), a 50% chance of sharing half the HLA alleles (haploidentical), and a 25% chance of sharing none of the HLA alleles (HLA mismatch). Therefore, siblings often are tested first for HLA matching because there is a 1:4 chance they will be an exact match. However, unmatched siblings usually are not used for donation because their HLA alleles are not the same as the patient's **(Choice E)**.
  - **Unrelated donors**: Unrelated donors do not have the same genome as the patient but can have perfect or near-perfect HLA matching; however, extensive searching is often required. **Matched unrelated donors** generally are **best for congenital genetic conditions** because the genomic

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HLA alleles (haploidentical), and a 25% chance of sharing none of the HLA alleles (HLA mismatch). Therefore, siblings often are tested first for HLA matching because there is a 1:4 chance they will be an exact match. However, unmatched siblings usually are not used for donation because their HLA alleles are not the same as the patient's **(Choice E)**.

- **Unrelated donors**: Unrelated donors do not have the same genome as the patient but can have perfect or near-perfect HLA matching; however, extensive searching is often required. **Matched unrelated donors** generally are **best for congenital genetic conditions** because the genomic error that leads to the patient's condition will not usually be present in an unrelated individual.

Educational objective:

Patients who require stem cell transplantation due to a congenital genomic disease typically receive matched unrelated donor cells because they will have matched human leukocyte antigen alleles but will not have the genomic mutation that caused the condition.

Genetics	Hematology & Oncology	Bone marrow transplantation
Subject	System	Topic

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A 12-year-old boy has prolonged oral bleeding immediately after a tooth extraction. Despite several interventions, the bleeding persists for hours and stops only after desmopressin (DDAVP) administration. The patient has several dental caries due to excessive juice intake and inconsistent oral hygiene. He has no other medical problems and takes no medications. His father and paternal grandmother have also had excessive bleeding after dental procedures. Review of systems is positive for mild bruising on his legs. Which of the following is the most likely therapeutic mechanism of desmopressin for this patient's condition?

A. ~~Binding to renal tubular cell receptors~~ (2%)
B. Increase in endothelial protein release (65%)
C. Increase in liver protein synthesis (8%)
D. Inhibition of fibrinolysis (4%)
E. Vascular smooth muscle contraction (19%)

65%
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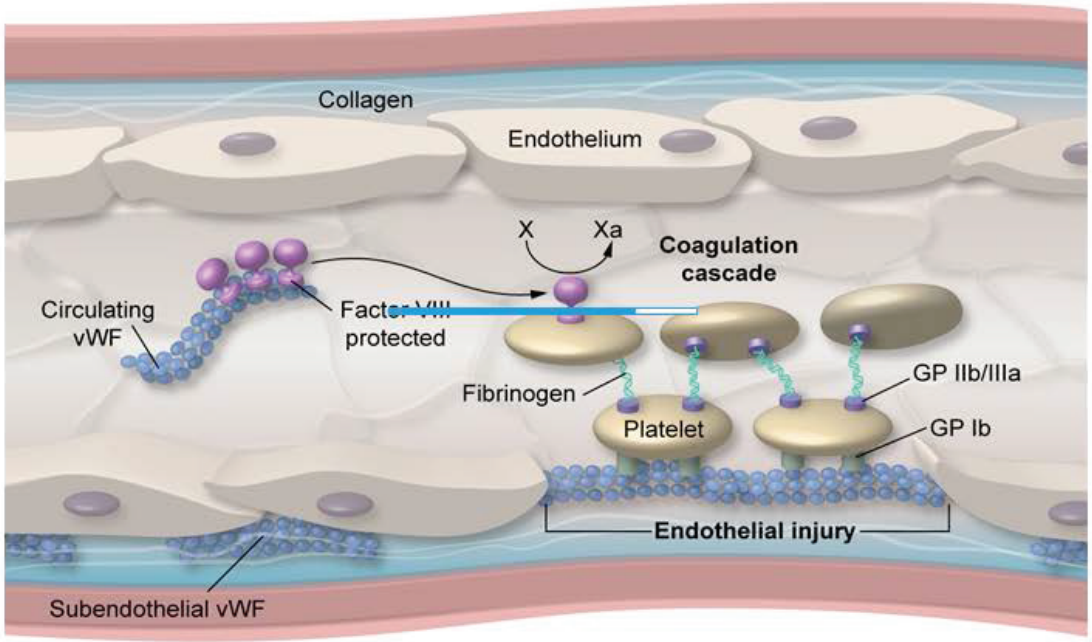
Effects of desmopressin (DDAVP) therapy	
Mild hemophilia A & Type 1 von Willebrand disease	Increases circulating factor VIII & endothelial secretion of vWF to stop bleeding
Central diabetes insipidus & Nocturnal enuresis	Binds to V2 receptors in renal tubular cells, leading to increased aquaporin channels, increased water reabsorption & decreased urine output
vWF = von Willebrand factor.	

This patient likely has **von Willebrand disease (vWD)**, an **autosomal dominant** deficiency of von Willebrand factor (vWF). **vWF** is secreted by **endothelial cells** and circulates in multimers that are non-covalently attached to clotting factor VIII, increasing its stability. vWF is also responsible for augmenting platelet binding at endothelial injury sites, which helps in the formation of the initial **platelet plug**. Patients

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Exhibit Display

Platelet adhesion & activation via von Willebrand factor



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platelet binding at endothelial injury sites, which helps in the formation of the initial **platelet plug**. Patients

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platelet binding at endothelial injury sites, which helps in the formation of the initial **platelet plug**. Patients have **increased bruisability** and **mucosal bleeding** (eg, oropharyngeal, gastrointestinal, uterine). Common manifestations include prolonged bleeding during dental procedures and heavy menstrual periods.

Most patients do not require medical attention as vWD symptoms are typically mild. However, those who need treatment can receive **desmopressin** (or 1-desamino-8-d-arginine vasopressin [DDAVP]), a synthetic analog of vasopressin (ie, antidiuretic hormone [ADH]), which is normally released by the posterior pituitary. DDAVP increases vWF release from endothelial cells.

DDAVP also raises factor VIII levels and is used for the treatment of mild hemophilia A. Hemophilia is an X-linked coagulation disorder and is unlikely in this patient given the clear autosomal dominant pattern of inheritance (father and paternal grandmother).

(Choice A) DDAVP also acts as an ADH analogue by binding to V2 receptors in the renal tubular cells, which leads to increased aquaporin channels, increased water reabsorption, and decreased urine output. Due to this action, DDAVP can be used in the treatment of central diabetes insipidus and nocturnal enuresis.

(Choice C) Although most clotting factors are synthesized in the liver, vWF and factor VIII are produced in

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enuresis.

(Choice C) Although most clotting factors are synthesized in the liver, vWF and factor VIII are produced in endothelial cells. DDAVP has no known effect on liver protein synthesis.

(Choice D) Inhibition of fibrinolysis (breaking down fibrin in blood clots) can decrease the rate of clot breakdown and potentially slow heavy bleeding. Aminocaproic acid is an anti-fibrinolytic medication used to treat excessive postoperative bleeding. DDAVP has no effect on the fibrinolytic system.

(Choice E) Vascular smooth muscle cells are involved in blood pressure regulation, with contraction leading to higher blood pressure. Endogenous vasopressin acts via the V1 vasopressin receptor to raise blood pressure through vascular smooth muscle contraction. Although DDAVP is chemically similar to vasopressin, it has a minimal effect on the V1 vasopressin receptor.

Educational objective:
The von Willebrand factor (vWF) enhances clotting through both augmentation of platelet binding and stabilization of factor VIII. Patients with von Willebrand disease are deficient in functional vWF and present with increased bruisability and prolonged mucosal bleeding. Desmopressin can alleviate bleeding through endothelial release of vWF.

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A 45-year-old man comes to the office for evaluation of fatigue that has been gradually increasing over the past 4 months. The patient has had difficulty keeping up with the labor involved with his job as a construction worker. Over the past 2 weeks, he has been unable to climb past the second floor of the building his company is renovating. The patient also has increasing shortness of breath with minor activities, such as lifting his toolbox out of the car. Review of systems reveals constipation and decreased concentration. Physical examination shows an overweight male with conjunctival pallor who has difficulty getting onto the examination table due to shortness of breath. Laboratory test results are as follows:

Complete blood count	
Hematocrit	26%
Mean corpuscular volume	72 fL
Ferritin	50 ng/mL (normal: 15-200 ng/mL)
Iron studies	
Iron	120 µg/dL (normal: 60-160 µg/dL)
Iron binding capacity	320 ug/dL (normal: 250-460 ug/dL)

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Ferritin	50 ng/mL (normal: 15-200 ng/mL)
Iron studies	
Iron	120 µg/dL (normal: 60-160 µg/dL)
Iron binding capacity	320 µg/dL (normal: 250-460 µg/dL)

Which of the following findings would most likely be seen on this patient's peripheral blood smear?

- A. Basophilic stippling (54%)
- B. ~~Heinz bodies~~ (5%)
- C. ~~Howell-Jolly bodies~~ (6%)
- D. Ring sideroblasts (22%)
- E. ~~Schistocytes~~ (10%)

Correct

54% Answered correctly

02 mins, 42 secs Time Spent

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Explanation

Lead poisoning in adults	
Risk factors	• Occupational exposure (eg, lead paint, batteries, ammunition, construction)
Clinical features	• Gastrointestinal (abdominal pain, constipation, anorexia) • Neurologic (cognitive deficits, peripheral neuropathy) • Hematologic (anemia)
Laboratory findings	• Anemia • Elevated venous lead level • Elevated serum zinc protoporphyrin level • Basophilic stippling on peripheral smear

This patient has **microcytic anemia**, **constipation**, and **mental status changes** in the setting of **construction work**. The most likely diagnosis is **lead poisoning**. Lead is a soft, heavy metal used for manufacturing a wide range of items, including batteries, alloys, and ammunition. Individuals working in

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	• Basophilic stippling on peripheral smear

This patient has **microcytic anemia**, **constipation**, and **mental status changes** in the setting of **construction work**. The most likely diagnosis is **lead poisoning**. Lead is a soft, heavy metal used for manufacturing a wide range of items, including batteries, alloys, and ammunition. Individuals working in these industries and others (eg, construction, mining, smelting, chemical processing, recycling, spray painting, radiator repair) can be regularly exposed to lead.

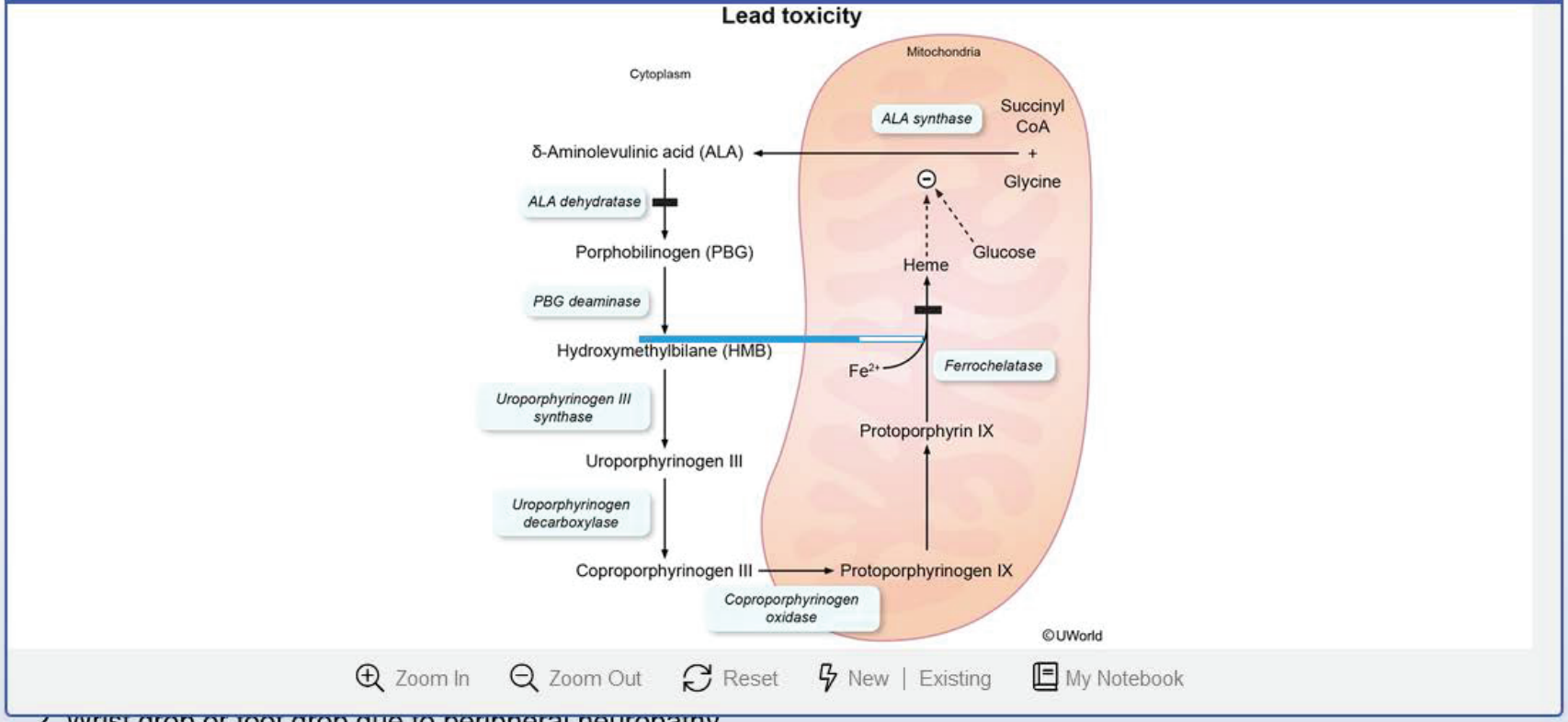
Lead inhibits the heme synthesis pathway (δ-aminolevulinate dehydratase and ferrochelatase), causing a microcytic, hypochromic anemia. Shortness of breath, particularly with exertion, occurs due to decreased oxygen delivery to peripheral tissues. Iron studies are normal unless co-existing iron deficiency is present as well. Basophilic stippling is frequently seen on peripheral blood smear. Inhibition of erythrocyte 5' nucleotidase by lead results in ribosome aggregation due to inability to degrade RNA, which is represented by coarse blue punctate dots in the cytoplasm of red blood cells (RBCs). Basophilic stippling is nonspecific and also seen in the thalassemias and myelodysplastic syndrome.

Adult lead poisoning can also have the following manifestations:

1. Bluish pigmentation ("lead line") at the gum-tooth line.
2. Wrist drop or foot drop due to peripheral neuropathy.

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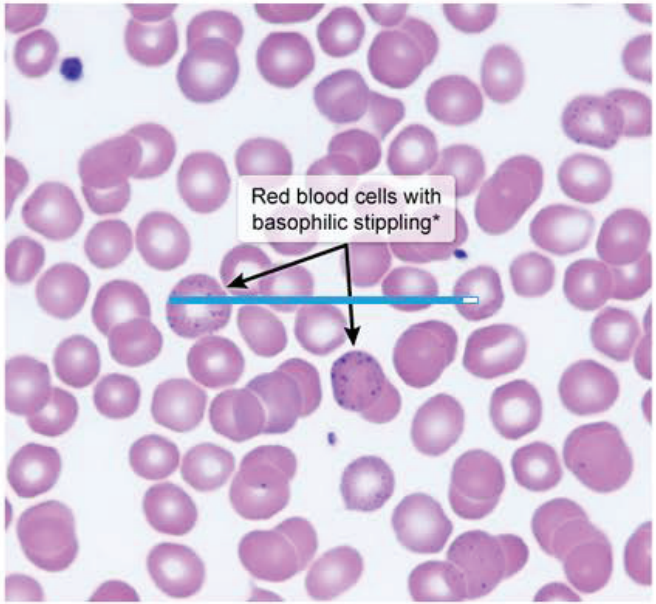
2. Wrist drop or foot drop due to peripheral neuropathy.

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Basophilic stippling



*Precipitated ribosomes

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2. Wrist drop or foot drop due to peripheral neuropathy.

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Adult lead poisoning can also have the following manifestations:

1. Bluish pigmentation ("lead line") at the gum-tooth line.
2. Wrist drop or foot drop due to peripheral neuropathy.

(Choice B) Heinz bodies are inclusions of denatured hemoglobin most commonly seen after oxidant stress in patients with glucose-6-phosphate dehydrogenase deficiency.

(Choice C) Howell-Jolly bodies are nuclear DNA remnant inclusions in peripheral RBCs that are normally removed by the spleen during circulation. The presence of Howell-Jolly bodies indicates decreased or absent splenic function (eg, post-splenectomy).

(Choice D) Ring sideroblasts are formed from precipitation of iron granules in developing erythrocytes due to defects in the heme synthesis pathway, including enzymatic inhibition induced by lead poisoning. Ring sideroblasts are seen in the bone marrow but not in the peripheral blood smear.

(Choice E) Schistocytes are fragmented parts of RBCs formed from mechanical hemolysis via sheer force of blood flow. Hemolytic uremic syndrome, thrombotic thrombocytopenic purpura, and disseminated intravascular coagulation all present with schistocytes.

Educational objective:

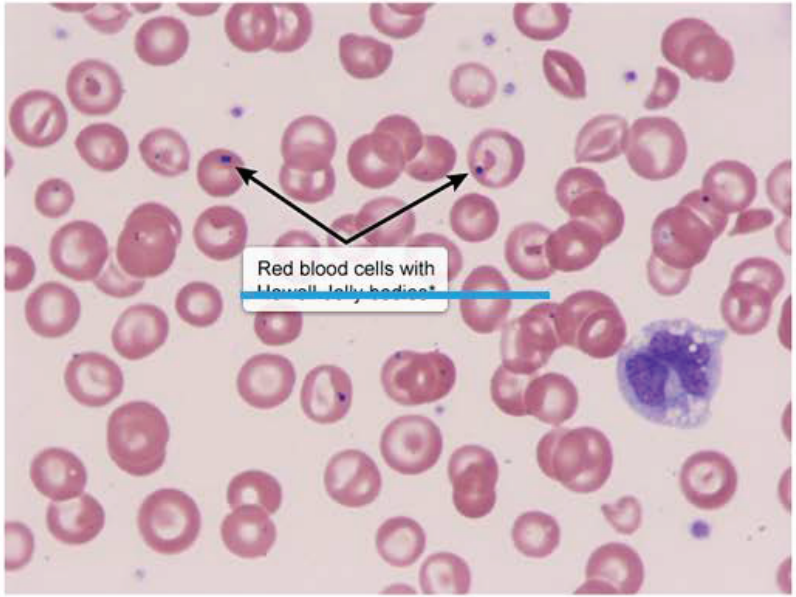
Lead poisoning in adults typically occurs through occupational exposure. Symptoms include colicky

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Adult lead poisoning can also have the following manifestations:

Exhibit Display

Howell-Jolly bodies



*Nuclear remnants associated with asplenia or hyposplenia

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Lead poisoning in adults typically occurs through occupational exposure. Symptoms include colicky

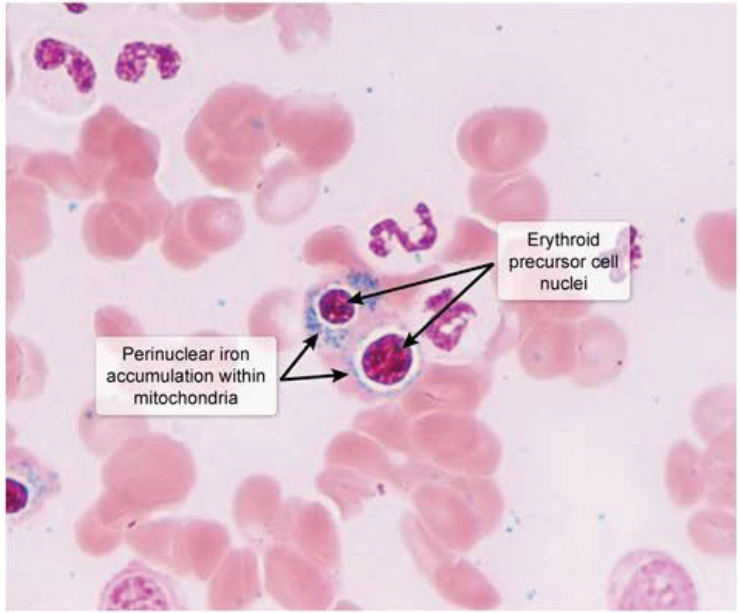
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Adult lead poisoning can also have the following manifestations:

Exhibit Display

Ring sideroblasts



Bone marrow aspirate – Prussian blue stain

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Lead poisoning in adults typically occurs through occupational exposure. Symptoms include colicky

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(Choice C) Howell-Jolly bodies are nuclear DNA remnant inclusions in peripheral RBCs that are normally removed by the spleen during circulation. The presence of Howell-Jolly bodies indicates decreased or absent splenic function (eg, post-splenectomy).

(Choice D) Ring sideroblasts are formed from precipitation of iron granules in developing erythrocytes due to defects in the heme synthesis pathway, including enzymatic inhibition induced by lead poisoning. Ring sideroblasts are seen in the bone marrow but not in the peripheral blood smear.

(Choice E) Schistocytes are fragmented parts of RBCs formed from mechanical hemolysis via sheer force of blood flow. Hemolytic uremic syndrome, thrombotic thrombocytopenic purpura, and disseminated intravascular coagulation all present with schistocytes.

Educational objective:

Lead poisoning in adults typically occurs through occupational exposure. Symptoms include colicky abdominal pain, constipation, lead lines on the gum, peripheral neuropathy, and anemia. Laboratory testing shows microcytic anemia with normal iron studies, and peripheral blood smear may reveal basophilic stippling.

References

- Lead toxicity.

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A 6-year-old boy is brought to the emergency department due to bleeding after a dental extraction earlier this morning. The patient's past medical history is significant for painful swelling of his knee joints after minor trauma. Aspiration of the joints during several occasions yielded frank blood, and he was diagnosed with hemarthrosis. He has no known allergies. Currently, hemostasis in this patient most likely can be achieved by the administration of which of the following?

A. ~~Factor XII~~ (15%)
B. Fibrinogen (15%)
C. ~~Protein C~~ (9%)
D. Thrombin (57%)
E. Urokinase (2%)

Correct

57%
Answered correctly

01 min, 15 secs
Time Spent

12/18/2020
Last Updated

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A history of prolonged bleeding following procedures (eg, dental extractions, surgeries) and spontaneous hemorrhages into the joints (hemarthrosis) is typical for **hemophilia**, an X-linked recessive bleeding disorder due to decreased levels of factor VIII (hemophilia A) or factor IX (hemophilia B).

Factors VIII and IX are components of the **intrinsic** coagulation pathway and activate factor X; activated factor X (Xa) then catalyzes the conversion of prothrombin (factor II) into thrombin as part of the final common pathway. In the absence of factors VIII or IX, activation of factor X and subsequent conversion of prothrombin into thrombin do not occur. Administration of **thrombin**, however, will make up for the deficiency and lead to blood clotting. In practice, prothrombin complex concentrates (containing factors II, VII, IX, and X, which lead to thrombin formation) were used for management of hemophilia B, although thrombogenic risks have limited their application.

In both types of hemophilia, the bleeding time and platelet count are normal. The prothrombin time (PT) is also normal as it tests the **e**xtrinsic clotting pathway and reflects the function of factors II, V, VII, and X (mnemonic: P**e**T). However, the activated partial thromboplastin time (PTT) is prolonged as it assesses the activity of factors II, V, VIII, IX, X, XI and XII, the **i**ntrinsic clotting pathway (mnemonic: P**i**TT). Diagnoses of hemophilia A and B are made by measuring plasma levels of factors VIII and IX, respectively.

(Choice A) Factor XII (Hageman) is synthesized by the liver and is activated by endothelial injury. It

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(Choice A) Factor XII (Hageman) is synthesized by the liver and is activated by endothelial injury. It triggers the intrinsic coagulation pathway by activating factor XI. The addition of factor XII does not clot the blood of patients with hemophilia because the downstream clotting factors VIII or IX are deficient.

(Choice B) Fibrinogen is a protein synthesized by the liver. Thrombin mediates cleavage of fibrinogen to form fibrin, the main component of thrombi; therefore, without thrombin, fibrinogen administration alone would not be helpful.

(Choice C) Protein C is a vitamin K-dependent factor synthesized in the liver. It is a physiologic anticoagulant that degrades factors Va and VIIIa.

(Choice E) Urokinase is a thrombolytic agent used for treatment of myocardial infarction and pulmonary embolism. It acts by converting plasminogen to plasmin, which then breaks down fibrinogen and fibrin into their respective degradation products. The addition of urokinase would prevent thrombosis.

Educational objective:
Bleeding after a tooth extraction and history of hemarthrosis are suggestive of hemophilia. Decreased levels of factor VIII or IX lead to failure to convert prothrombin into thrombin and deficient thrombus formation. The addition of thrombin to the blood of a patient with hemophilia results in clotting.

References

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A 34-year-old man is brought to the hospital by ambulance after being involved in a motor vehicle collision. He was an unrestrained passenger and sustained considerable trauma. On arrival to the emergency department, he is hypotensive and bleeding from several sites. The patient receives an emergency blood transfusion as part of the resuscitation efforts. Abdominal ultrasound reveals splenic laceration and blood in the peritoneal cavity. En route to the operating room, the patient develops difficulty breathing, chills, and pain in the chest and back. Urine drainage from the Foley catheter was initially clear but now appears brown in color. Which of the following is the most likely cause of this patient's new findings?

A. ~~CD8+ lymphocyte-mediated cytotoxicity~~ (9%)

✓ B. Complement-mediated cell lysis (50%)

C. ~~Endotoxin-induced TNF-α surge~~ (8%)

D. ~~IgE-mediated reaction to serum proteins~~ (18%)

E. Vascular deposition of immune complexes (13%)

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Hypersensitivity reactions			
	Humoral components	**Cellular components**	**Examples**
Type I (immediate)	• **IgE**	• Basophils • Mast cells	• Anaphylaxis • Allergies
Type II (cytotoxic)	• **IgG & IgM** autoantibodies • Complement activation	• NK cells • Eosinophils • Neutrophils • Macrophages	• Autoimmune hemolytic anemia • Goodpasture syndrome
Type III (immune complex)	• Deposition of **antibody-antigen complexes**	• Neutrophils	• Serum sickness • PSGN • Lupus

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(cytotoxic)	• Complement activation	• Neutrophils • Macrophages	• Goodpasture syndrome
Type III (immune complex)	• Deposition of **antibody-antigen complexes** • Complement activation	• Neutrophils	• Serum sickness • PSGN • Lupus nephritis
Type IV (delayed type)	• None	• **T cells** • **Macrophages**	• Contact dermatitis • Tuberculin skin test

NK = natural killer; **PSGN** = poststreptococcal glomerulonephritis.

This patient is most likely experiencing an **acute hemolytic transfusion reaction**. This condition presents with **fever and chills**, hypotension, dyspnea, **chest and/or back pain**, and **hemoglobinuria** (red- to brown-colored urine). Patients may also develop disseminated intravascular coagulation and renal failure

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This patient is most likely experiencing an **acute hemolytic transfusion reaction**. This condition presents with **fever and chills**, hypotension, dyspnea, **chest and/or back pain**, and **hemoglobinuria** (red- to brown-colored urine). Patients may also develop disseminated intravascular coagulation and renal failure. Acute hemolytic reactions occur within **minutes to hours** of starting a blood transfusion and are most often due to ABO incompatibility between the donor and recipient. These reactions can be fatal and require **immediate cessation** of the transfusion when the diagnosis is suspected.

Acute hemolytic transfusion reactions are an example of an **antibody-mediated (type II)** hypersensitivity reaction. Anti-ABO antibodies (mainly IgM) in the recipient bind the corresponding antigens on transfused donor erythrocytes, leading to complement activation. Anaphylatoxins (C3a and C5a) cause vasodilatation and symptoms of shock, while formation of the membrane attack complex (C5b-C9) leads to **complement-mediated cell lysis**. Hemolytic disease of the newborn due to Rh-incompatibility is another example of type II hypersensitivity.

(Choice A) Cytotoxic $CD8^+$ T-lymphocytes are responsible for destroying cells infected with intracellular pathogens (eg, viruses). Recognition of an antigen-MHC class I complex by the T-cell receptor activates $CD8^+$ lymphocytes, which then initiate apoptosis of the infected cell.

(Choice C) TNF-α is produced by macrophages in response to bacterial endotoxin and causes symptoms

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(Choice C) TNF-α is produced by macrophages in response to bacterial endotoxin and causes symptoms of septic shock (eg, fever, hypotension, and tachycardia) when released in large amounts. Transfusion transmitted bacterial infection could cause septic shock, but it would not result in hemoglobinuria.

(Choice D) Allergic transfusion reactions are IgE-mediated (type I) hypersensitivity reactions against plasma proteins found in transfused blood. They can be mild (urticaria, itching) or result in severe anaphylaxis (most common in IgA-deficient patients with anti-IgA antibodies).

(Choice E) Vascular deposition of immune complexes is an example of type III hypersensitivity. In conditions such as systemic lupus erythematosus and rheumatoid arthritis, antigen-antibody complexes deposit in various tissues and activate complement, causing tissue inflammation and destruction.

Educational objective:
Acute hemolytic transfusion reaction is a antibody-mediated (type II) hypersensitivity reaction caused by pre-existing anti-ABO antibodies that bind antigens on transfused donor erythrocytes. Subsequent complement activation results in erythrocyte lysis, vasodilation, and symptoms of shock. Common findings include fever, hypotension, chest and back pain, and hemoglobinuria.

Immunology	Hematology & Oncology	Hypersensitivity reactions
Subject	System	Topic

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An infant born to a Greek immigrant appears healthy at birth but develops transfusion-dependent hemolytic anemia by the age of 6 months. His erythrocytes contain insoluble aggregates of hemoglobin subunits. The child developed normally in utero because at that time he produced high quantities of:

A. α-globin (3%)
B. β-globin (3%)
C. γ-globin (84%)
D. δ-globin (5%)
E. ζ-globin (3%)

Correct

84% Answered correctly

30 secs Time Spent

01/30/2021 Last Updated

Explanation

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In adults, hemoglobin A is the predominant form of hemoglobin. It is a tetramer consisting of two alpha and two beta chains. Normally the synthesis of alpha and beta chains is tightly regulated such that one α-chain is synthesized for every β-chain. Hemoglobin formation begins within a few weeks of conception. The initial hemoglobin formed by a fetus in utero is called embryonic hemoglobin (Gower). This hemoglobin is composed of two zeta (ζ) and two epsilon (ε) chains (ζ2ε2) and is produced in the embryonic yolk sac. Within a few weeks the fetal liver starts synthesizing hemoglobin F (fetal hemoglobin). This form of hemoglobin is composed of two alpha and two gamma chains (α2γ2). HbF is the major hemoglobin in the fetus during last few months of gestation and in infants during first few weeks of postnatal life. HbA synthesis starts during the final month of gestation and gradually replaces HbF during postnatal life. Knowing the chronology of fetal hemoglobin formation and the gradual transition to adult hemoglobin (HbA) is important in understanding the relationship between clinical manifestations and postnatal age in beta thalassemia.

Thalassemias are hereditary hemolytic anemias resulting from defective synthesis of globin chains. As described above, the synthesis of alpha and beta globin chains is very coordinated. In patients with thalassemia, the synthesis of either alpha or beta chains is defective. Beta thalassemia is caused by defective synthesis of beta chains. There are two copies of the beta globin gene (one from each parent). If

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described above, the synthesis of alpha and beta globin chains is very coordinated. In patients with thalassemia, the synthesis of either alpha or beta chains is defective. Beta thalassemia is caused by defective synthesis of beta chains. There are two copies of the beta globin gene (one from each parent). If only one gene is defective the patient will have beta thalassemia trait (beta thalassemia minor) and lack significant anemia. A defect in both beta globin genes results in severe hemolytic anemia known as beta thalassemia major. In this disease, alpha chains are produced normally but they cannot form stable tetramers due to the lack of beta globin chains. This failure to form stable hemoglobin leads to precipitation of alpha globin chains and premature lysis of red blood cells. Beta thalassemia cannot become symptomatic as long as there are significant amounts of gamma chains present because gamma chains make up for the absence of HbA beta chains in forming tetramers. Thus, in late gestation and early postnatal life, the expression of hemoglobin A is offset by gamma chain production **(Choice C)**. As gamma chain production wanes, patients will become symptomatic.

(Choice A) α-globin is a normal component of both HbA and HbF. α-globin synthesis is defective in α-thalassemia but it is normal in β-thalassemia. α-globin is able to combine with γ-globin to form HbF. This allows patients with β-thalassemia major to be asymptomatic in utero and in the first few months following birth.

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(Choice A) α-globin is a normal component of both HbA and HbF. α-globin synthesis is defective in α-thalassemia but it is normal in β-thalassemia. α-globin is able to combine with γ-globin to form HbF. This allows patients with β-thalassemia major to be asymptomatic in utero and in the first few months following birth.

(Choice B) β-globin synthesis is defective in patients with b-thalassemia.

(Choice D) δ-globin is a minor globin gene that is expressed at very low levels in normal adults. Two α-globins and two δ-globins combine to form hemoglobin A2.

(Choice E) ζ-globin is a component of hemoglobin Gower, the initial hemoglobin formed by the embryo very early in embryogenesis.

Educational Objective:
HbF contains γ-globin instead of β-globin. Patients with homozygotic β-thalassemia (β-thalassemia major) are asymptomatic at birth due to the presence of γ-globins and HbF. Switching to HbA production and the cessation of γ-globin synthesis precipitates the symptoms of β-thalassemia.

Biochemistry	Hematology & Oncology	Thalassemia
Subject	System	Topic

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A 65-year-old man comes to the office due to several months of severe fatigue that limits his ability to do daily activities. He has also had upper abdominal fullness, early satiety, and unintentional weight loss but no fever, night sweats, cough, or rash. The patient has not seen a physician for many years. He does not use tobacco, alcohol, or illicit drugs and is a retired chemical engineer. Physical examination shows mucosal pallor with no scleral icterus. The lungs are clear on auscultation, and heart sounds are normal. There is mild hepatomegaly, and the spleen tip is palpable close to the midline of the abdomen. Laboratory evaluation reveals pancytopenia. Peripheral blood smear shows immature granulocytes, nucleated erythrocytes, and teardrop cells. Bone marrow aspiration is attempted but yields no marrow. Which of the following histopathological features is most likely to be present in this patient's spleen?

A. Accumulation of macrophages with fibrillary cytoplasm (9%)

B. ~~Diffuse neutrophilic infiltration and follicular necrosis~~ (3%)

C. ~~Dilated sinusoids and fibrous nodules with hemosiderin~~ (15%)

✓ D. Large islands of hematopoietic progenitor cells (69%)

E. ~~Numerous noncaseating epithelioid granulomas~~ (1%)

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Explanation

Primary myelofibrosis	
Pathogenesis	Chronic myeloproliferative disorder with **clonal megakaryocytes** → secrete transforming growth factor-ß → stimulates fibroblasts in BM to produce collagen → **BM fibrosis** → hematopoietic stem cells migrate to liver & spleen → **extramedullary hematopoiesis**
Manifestations	• Severe fatigue • Hepatomegaly + **massive splenomegaly** (can compress stomach) • ≥1 cytopenias • **Dacrocytes** (teardrop cells) on peripheral blood smear • BM aspiration – often **dry tap** due to fibrosis

BM = bone marrow.

Primary myelofibrosis is a chronic myeloproliferative disorder marked by the clonal expansion of atypical

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BM = bone marrow.

Primary myelofibrosis is a chronic myeloproliferative disorder marked by the clonal expansion of atypical megakaryocytes. These atypical cells produce transforming growth factor-beta, which stimulates fibroblasts in the bone marrow to lay down collagen, leading to subsequent **bone marrow fibrosis**. Because fibrotic bone marrow is inhospitable to hematopoietic stem and progenitor cells, these precursor cells migrate out of the bone marrow to the liver and spleen, the primary sites of **extramedullary hematopoiesis**.

The proliferation of erythroid, myeloid, and megakaryocytic **progenitor cells in the spleen** leads to a marked expansion of the splenic red pulp and usually results in **dramatic splenomegaly**. Nucleated red cells and immature granulocytes spill into the circulation and can be identified on peripheral blood smear. Dacrocytes are also common due to erythrocyte membrane damage during red blood cell production in the spleen or fibrotic marrow. Because extramedullary hematopoiesis is less efficient than medullary hematopoiesis, patients typically have one or more **cytopenias**.

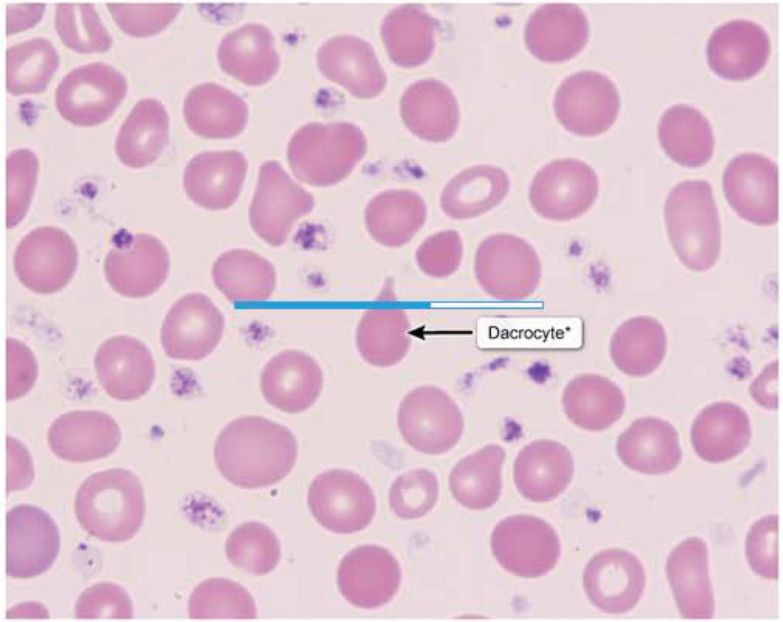
The diagnosis of primary myelofibrosis requires bone marrow evaluation. Aspiration of bone marrow is frequently unsuccessful (**dry tap**) due to fibrosis. Therefore, bone marrow biopsy is generally required and usually shows hypocellular marrow with significant fibrosis and atypical megakaryocytes. A minority of

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Primary myelofibrosis

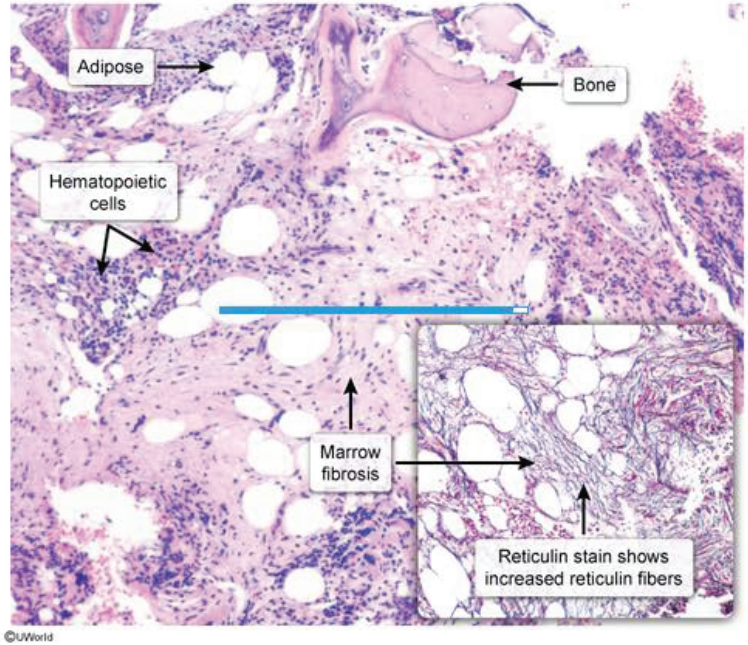


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Primary myelofibrosis



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usually shows hypocellular marrow with significant fibrosis and atypical megakaryocytes. A minority of primary myelofibrosis cases have been linked to chemical exposure (eg, toluene, benzene).

(Choice A) Gaucher disease is an autosomal recessive lysosomal storage disease associated with hepatosplenomegaly and pancytopenia due to the accumulation of glucocerebroside within the cytoplasm of macrophages (crumpled-paper appearance). However, most cases present in childhood. In addition, a dry tap on bone marrow aspirate and dacrocytes on peripheral smear would be atypical.

(Choice B) Acute infections of the spleen (eg, septic emboli from infective endocarditis) are typically associated with diffuse neutrophilic infiltration. Follicular necrosis is also common if the infection is due to group A *Streptococcus*. A dry tap, dacrocytes, and lack of fever make this less likely.

(Choice C) Congestive splenomegaly due to portal hypertension (eg, from liver cirrhosis) is associated with dilated sinusoids, fibrosis of the red pulp, and hemosiderin-laden macrophages. A dry tap and dacrocytes would not be seen.

(Choice E) Splenic noncaseating granulomas are common in sarcoidosis, some malignancies, and some infectious disorders. However, a dry tap and dacrocytes make primary myelofibrosis far more likely.

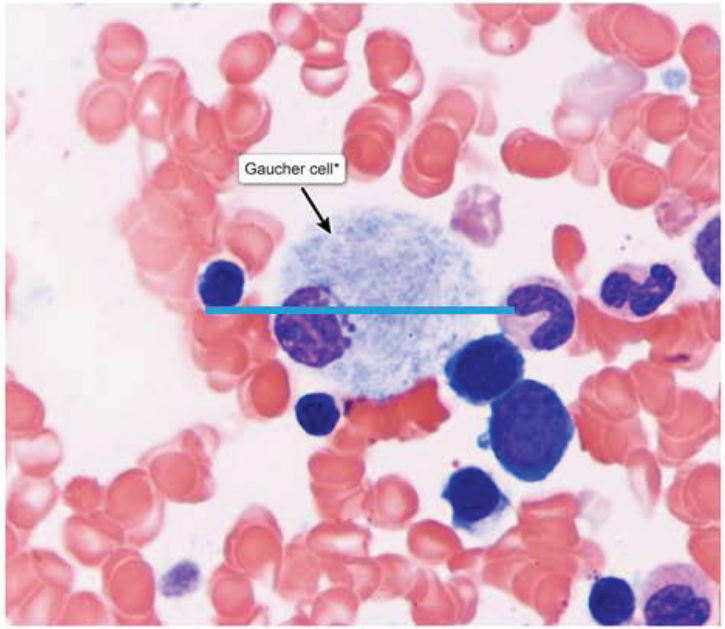
Educational objective:
Primary myelofibrosis is a chronic myeloproliferative disorder associated with bone marrow fibrosis.

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usually shows hypocellular marrow with significant fibrosis and atypical megakaryocytes. A minority of

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Gaucher disease



*"Wrinkled tissue paper" cytoplasm due to glucocerebroside accumulation

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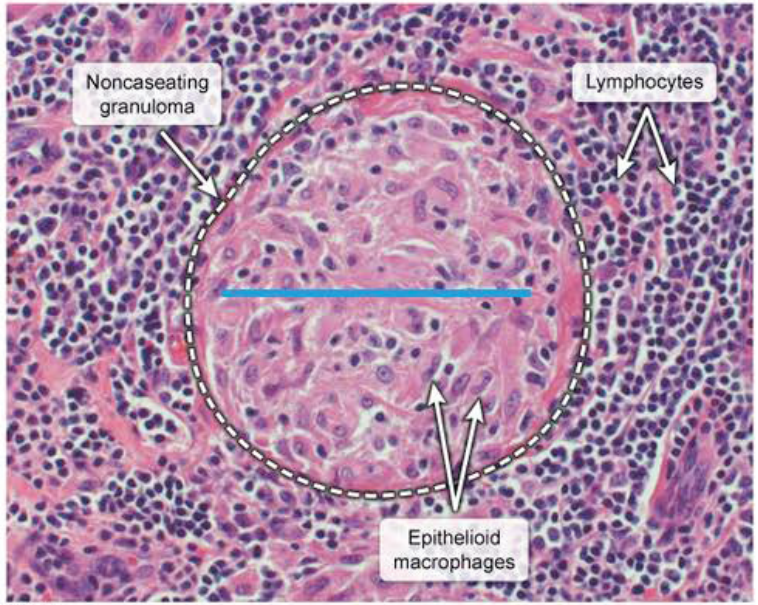
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usually shows hypocellular marrow with significant fibrosis and atypical megakaryocytes. A minority of

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Sarcoidosis



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(Choice B) Acute infections of the spleen (eg, septic emboli from infective endocarditis) are typically associated with diffuse neutrophilic infiltration. Follicular necrosis is also common if the infection is due to group A *Streptococcus*. A dry tap, dacrocytes, and lack of fever make this less likely.

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Educational objective:

Primary myelofibrosis is a chronic myeloproliferative disorder associated with bone marrow fibrosis. Extramedullary hematopoiesis leads to marked expansion of the splenic red pulp with hematopoietic progenitor cells, resulting in massive splenomegaly. Patients also usually have hepatomegaly, cytopenias, and peripheral smear abnormalities (eg, dacrocytes, nucleated red cells, immature granulocytes).

References

- Homeostatic and pathogenic extramedullary hematopoiesis.

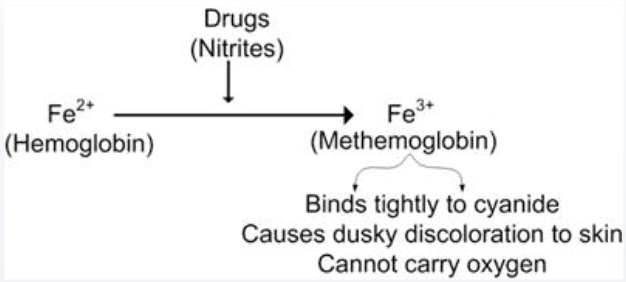
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A 34-year-old industry worker experiences rapid-onset shortness of breath, dizziness, palpitations, and flushed skin after accidental exposure to chemical fumes. Examination by an occupational physician shows that the patient is tachypneic and has a reddish discoloration of the skin without cyanosis. The patient is immediately instructed to inhale amyl nitrite from the safety kit. The success of this antidote is dependent upon its ability to convert hemoglobin into a form with increased affinity for which of the following substances?

A. 2,3-biphosphoglycerate (23%)
B. Carbon dioxide (9%)
C. Carbon monoxide (8%)
D. Cyanide (50%)
E. Iron (6%)
F. Lead (0%)

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The toxicity of **cyanide** is dependent upon its ability to bind **ferric iron** (Fe^{3+}) with high affinity, inhibiting **cytochrome c oxidase** in the mitochondria. This electron transport chain enzyme is essential for oxidative phosphorylation; inhibition results in severe lactic acidosis and death as a result of cells switching to anaerobic metabolism.

Cyanide poisoning presents with **reddish skin discoloration**, tachypnea, headache, and tachycardia, often accompanied by nausea/vomiting, confusion, and weakness. Symptoms develop rapidly and can quickly progress to seizures and cardiovascular collapse. Laboratory studies indicate severe **lactic acidosis** in conjunction with a **narrowing of the venous-arterial PO_2 gradient**, resulting from the inability of tissue to extract arterial oxygen.

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Administration of **inhaled amyl nitrite** oxidizes ferrous iron (Fe^{2+}) present in hemoglobin to ferric iron (Fe^{3+}), generating **methemoglobin**. Methemoglobin is incapable of carrying oxygen but has a high affinity for cyanide; it binds and sequesters cyanide in the blood, freeing it from cytochrome oxidase and limiting its toxic effects. Hydroxycobalamin, a vitamin B_{12} precursor, and sodium thiosulfate are also antidotes for cyanide poisoning. Their interactions with cyanide generate relatively nontoxic metabolites that are easily excreted in the urine.

(Choices A and B) The presence of 2,3-biphosphoglycerate causes a right shift in the oxygen-hemoglobin dissociation curve, decreasing hemoglobin's affinity for oxygen and increasing its affinity for carbon dioxide.

(Choice C) Hemoglobin has a much higher affinity for carbon monoxide than it does for oxygen. This is the basis for carbon monoxide poisoning, which is treated with high-flow oxygen.

(Choice E) The affinity of hemoglobin for iron is not affected by nitrite administration, although nitrites do oxidize the heme iron to its Fe^{3+} state.

(Choice F) Lead poisoning causes defective heme synthesis. If lead is acutely ingested, chelation therapy with dimercaprol or edetate disodium calcium ($CaNa_2EDTA$) should be initiated.

Educational objective:

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dissociation curve, decreasing hemoglobin's affinity for oxygen and increasing its affinity for carbon dioxide.

(Choice C) Hemoglobin has a much higher affinity for carbon monoxide than it does for oxygen. This is the basis for carbon monoxide poisoning, which is treated with high-flow oxygen.

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(Choice F) Lead poisoning causes defective heme synthesis. If lead is acutely ingested, chelation therapy with dimercaprol or edetate disodium calcium ($CaNa_2EDTA$) should be initiated.

Educational objective:
Nitrites are oxidizing agents that are effective in treating cyanide poisoning due to their ability to induce methemoglobinemia. Methemoglobin contains ferric (Fe^{3+}) rather than ferrous iron (Fe^{2+}). Cyanide binds to ferric iron more avidly than to mitochondrial cytochrome enzymes, diminishing cyanide's toxic effect.

Biochemistry	Hematology & Oncology	Cyanide poisoning
Subject	System	Topic

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A 24-year-old man comes to the clinic due to 2 weeks of progressive generalized weakness. He has also had significant bruising on his trunk that developed spontaneously without trauma. The patient has no known medical conditions and takes no medications. Temperature is 37.1 C (98.8 F), pulse is 120/min, and respirations are 20/min. Conjunctival pallor is present. Cardiac examination reveals mild sinus tachycardia with no murmurs. Skin examination shows truncal ecchymoses but is otherwise normal. Laboratory results reveal a hemoglobin of 6.8 g/dL and a normal creatinine. Bone marrow aspiration is grossly pale and histologically appears diluted due to high lipid content. Which of the following laboratory patterns is most likely present in this patient?

	Erythropoietin	Reticulocytes	Mean corpuscular volume	Haptoglobin	
A.	↑	↑	Normal	Low	(9%)
B.	↑	↓	Normal	Normal	(65%)
C.	↑	↓	↓	High	(15%)

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reveal a hemoglobin of 6.6 g/dL and a normal creatinine. Bone marrow aspiration is grossly pale and histologically appears diluted due to high lipid content. Which of the following laboratory patterns is most likely present in this patient?

	Erythropoietin	Reticulocytes	Mean corpuscular volume	Haptoglobin	
A.	↑	↑	Normal	Low	(9%)
✓ B.	↑	↓	Normal	Normal	(65%)
C.	↑	↓	↓	High	(15%)
D.	↓	↑	↓	Low	(3%)
E.	↓	↓	Normal	Normal	(6%)

Correct

65% Answered correctly

01 min, 49 secs Time Spent

11/11/2020 Last Updated

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Aplastic anemia	
Pathogenesis	Bone marrow failure due to hematopoietic stem cell deficiency ($CD34^+$)
Causes	• Autoimmune • Infections (eg, HIV, Epstein-Barr virus) • Drugs (eg, carbamazepine, chloramphenicol, sulfonamides) • Exposure to radiation or toxins (eg, benzene, solvents)
Clinical & laboratory findings	Laboratory studies: pancytopenia • Anemia (fatigue, weakness, pallor) • Thrombocytopenia (mucosal bleeding, easy bruising, petechiae) • Leukopenia (recurrent infections) Biopsy: hypocellular bone marrow with fat & stromal cells

This patient with a **low hemoglobin level** has several symptoms of **anemia**, including generalized weakness, tachycardia, and conjunctival pallor. The presence of **spontaneous bruising** in the absence of trauma likely indicates **thrombocytopenia**. Bone marrow aspirate reveals an abundance of lipids instead

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This patient with a **low hemoglobin level** has several symptoms of **anemia**, including generalized weakness, tachycardia, and conjunctival pallor. The presence of **spontaneous bruising** in the absence of trauma likely indicates **thrombocytopenia**. Bone marrow aspirate reveals an abundance of lipids instead of cells, which is usually seen with **bone marrow aplasia or hypoplasia**. This constellation of findings is highly suggestive of **aplastic anemia** (AA).

AA is a form of bone marrow failure primarily caused by cytotoxic T-cell destruction of multipotent hematologic stem cells. Because multipotent stem cells produce all mature blood cells, patients usually develop **pancytopenia** (not just anemia as the name suggests) and have manifestations of anemia, thrombocytopenia, and/or leukopenia (eg, infections).

As with most forms of anemia, anemia-induced tissue hypoxia stimulates interstitial cells in the kidney to **increase the release of erythropoietin**. However, in AA, erythropoietin is unable to stimulate significant new red blood cell production due to the reduced population of functioning hematologic stem cells; therefore, **reticulocytes are inappropriately low**. Because the blood cells produced by the remaining undamaged hematopoietic stem cells are normal in morphology, erythrocytes are normal in size and appearance; therefore, **mean corpuscular volume is normal**. Because there is no intravascular hemolysis, **haptoglobin** (binds free hemoglobin in the blood) is also **normal**.

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increase the release of erythropoietin. However, in AA, erythropoietin is unable to stimulate significant new red blood cell production due to the reduced population of functioning hematologic stem cells; therefore, **reticulocytes are inappropriately low**. Because the blood cells produced by the remaining undamaged hematopoietic stem cells are normal in morphology, erythrocytes are normal in size and appearance; therefore, **mean corpuscular volume is normal**. Because there is no intravascular hemolysis, **haptoglobin** (binds free hemoglobin in the blood) is also **normal**.

Educational objective:

Aplastic anemia (AA) is a form of bone marrow failure associated with pancytopenia and bone marrow aplasia/hypoplasia. Although erythropoietin levels are high, reticulocytes remain low because the production of new erythrocytes is impaired by a paucity of bone marrow stem cells. However, the blood cells produced by the remaining stem cells are normal in morphology and red cell indexes (eg, mean corpuscular volume) are usually normal.

Pathology	Hematology & Oncology	Aplastic anemia
Subject	System	Topic

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A 5-year-old girl is brought to the emergency department for evaluation of a rash. Her mother noticed a few red spots on the child's cheeks this morning, which subsequently spread to the neck and trunk as the day progressed. The patient has a history of partial complex seizures, which have been well controlled with carbamazepine. Vital signs are normal. The lips are slightly pale, and the oropharynx is clear. There is no lymphadenopathy. The abdomen is soft with no palpable masses or hepatosplenomegaly. Skin examination shows flat, red, pinpoint lesions that do not blanch on the face, neck, trunk, and extremities. Neurological examination is unremarkable. Laboratory results are as follows:

Complete blood count

Hemoglobin	9.5 g/dL
Platelets	25,000/mm^3
Leukocytes	2,900/mm^3

Peripheral smear reveals a paucity of cells with normal morphologic appearance of all cell lines. Which of the following mechanisms is most likely responsible for this patient's current condition?

A. Autoantibodies against hematopoietic stem cells (17%)

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Complete blood count

Hemoglobin	9.5 g/dL
Platelets	25,000/mm^3
Leukocytes	2,900/mm^3

Peripheral smear reveals a paucity of cells with normal morphologic appearance of all cell lines. Which of the following mechanisms is most likely responsible for this patient's current condition?

A. Autoantibodies against hematopoietic stem cells (17%)
B. Impaired DNA synthesis due to vitamin deficiency (2%)
C. Medication-associated adverse effect (66%)
D. Peripheral cell sequestration in splenic sinusoids (3%)
E. Thrombotic microangiopathic hemolysis (8%)

66% 01 min, 56 secs 12/02/2020

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Explanation

Aplastic anemia	
Pathogenesis	Bone marrow failure due to hematopoietic stem cell deficiency ($CD34^+$)
Causes	• Autoimmune • Infections (eg, HIV, Epstein-Barr virus) • Drugs (eg, carbamazepine, chloramphenicol, sulfonamides) • Exposure to radiation or toxins (eg, benzene, solvents)
Clinical & laboratory findings	Laboratory studies: pancytopenia • Anemia (fatigue, weakness, pallor) • Thrombocytopenia (mucosal bleeding, easy bruising, petechiae) • Leukopenia (recurrent infections) Biopsy: hypocellular bone marrow with fat & stromal cells

This patient who takes carbamazepine developed pancytopenia with morphologically normal peripheral

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	Biopsy: hypocellular bone marrow with fat & stromal cells

This patient who takes carbamazepine developed pancytopenia with morphologically normal peripheral blood cells, indicating likely **drug-induced aplastic anemia** (AA). AA is a form of **bone marrow failure** caused by damage to **multipotent hematopoietic stem cells**. Most cases are induced by direct toxicity to hematopoietic stem cells or an alteration to stem cell surface antigens, which leads to their subsequent destruction by cytotoxic lymphocytes.

Although AA can be idiopathic, it is often triggered by ionizing radiation, toxic chemicals, viral infections, or medications. Drug-induced AA is typically categorized as follows:

- **Dose-dependent reactions** are caused by medications (eg, chemotherapy, immunosuppressives) that are toxic to the bone marrow when drug levels exceed a certain concentration for a certain period. They tend to be predictable in onset.
- **Idiosyncratic reactions** are often caused by antiseizure medications (eg, **carbamazepine**, valproic acid), sulfonamides, or nifedipine. They are unpredictable, unrelated to the dose of the drug, and may occur at any point during or after therapy. Although the mechanism is unclear, patients often have genetic mutations in drug-metabolizing enzymes or efflux pumps, which may promote toxicity.

Because multipotent hematopoietic cells generate all mature blood cells, patients with AA usually have

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Because multipotent hematopoietic cells generate all mature blood cells, patients with AA usually have signs of thrombocytopenia (eg, **petechiae**, bleeding), anemia (eg, **pale mucous membranes**), and/or leukopenia (eg, infections). Bone marrow biopsy will reveal a hypocellular marrow with increased lipids.

(Choice A) AA is primarily caused by toxic injury to hematopoietic stem cells or cytotoxic T-cell-mediated stem cell destruction; autoantibodies are not a major part of the pathogenesis.

(Choice B) Vitamin B_{12} and folate deficiencies impair DNA synthesis in hematopoietic stem cells, which leads to hypersegmented neutrophils and macrocytic erythrocytes (not normal morphologic cells) on peripheral smear because of delayed nuclear (relative to cytoplasmic) maturation.

(Choice D) Hypersplenism can cause sequestration with increased destruction of blood cells in the splenic sinusoids. Most cases arise in those with portal hypertension (eg, liver disease, portal vein thrombosis), which leads to an increase in splenic volume and activity. Although cytopenias can occur, they are typically mild and do not cause symptoms; in addition, most patients have splenomegaly.

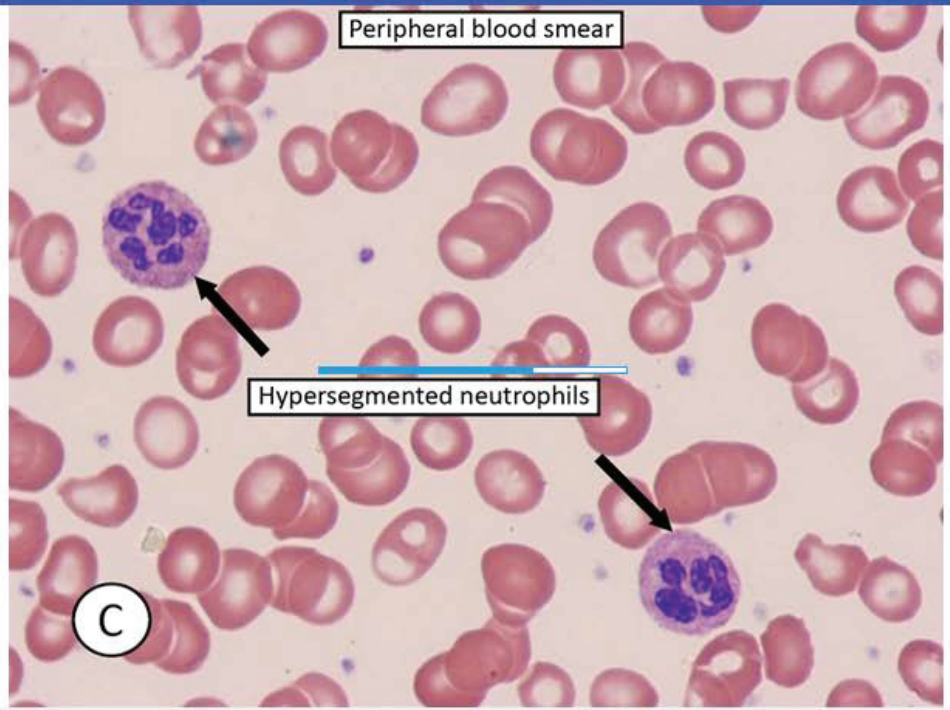
(Choice E) Thrombotic microangiopathic hemolysis is associated with clot formation in the microvasculature and shearing of red blood cells, leading to thrombocytopenia (eg, petechiae) and anemia. However, peripheral blood smear would reveal schistocytes.

Educational objective:

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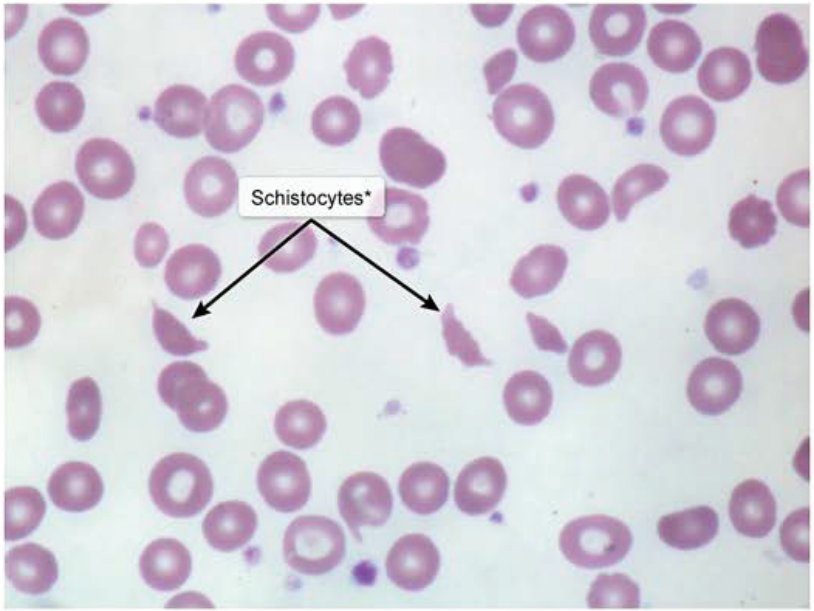
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Exhibit Display

Schistocytes



*Fragmented red blood cells

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peripheral smear because of delayed nuclear (relative to cytoplasmic) maturation.

(Choice D) Hypersplenism can cause sequestration with increased destruction of blood cells in the splenic sinusoids. Most cases arise in those with portal hypertension (eg, liver disease, portal vein thrombosis), which leads to an increase in splenic volume and activity. Although cytopenias can occur, they are typically mild and do not cause symptoms; in addition, most patients have splenomegaly.

(Choice E) Thrombotic microangiopathic hemolysis is associated with clot formation in the microvasculature and shearing of red blood cells, leading to thrombocytopenia (eg, petechiae) and anemia. However, peripheral blood smear would reveal schistocytes.

Educational objective:
Aplastic anemia (AA) is bone marrow failure due to multipotent hematopoietic stem cell destruction. Cases are often triggered by medications, radiation, toxins, or viruses. Medication-induced AA can be due to dose-dependent bone marrow damage (eg, chemotherapy, immunosuppressive drugs) or idiosyncratic reactions (eg, antiseizure medicines, sulfonamides, nifedipine) that may occur at any point during or after therapy.

Pharmacology	Hematology & Oncology	Aplastic anemia
Subject	System	Topic

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A 54-year-old woman comes to the office due to 3 months of progressive pain and prolonged morning stiffness in her hand joints. She has tried over-the-counter naproxen without significant relief. Review of systems is positive for fatigue. The patient has no other chronic medical conditions and takes no other medications regularly. Vital signs are normal. Swelling and tenderness of the proximal interphalangeal joints and metacarpophalangeal joints are present in both hands. Laboratory studies reveal a hemoglobin of 9.8 g/dL and MCV of 86. The patient is prescribed methotrexate therapy. Laboratory results 6 months later reveal that hemoglobin has increased to 12 g/dL. If measured, which of the following changes were most likely present in this patient before the start of methotrexate therapy?

	Circulating iron level	Bone marrow iron	
✓ A.	Low	High	(65%)
✗ B.	Low	Low	(16%)
C.	~~High~~	~~Low~~	(5%)
D.	~~High~~	~~High~~	(1%)

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This patient's polyarticular hand joint pain, swelling, and prolonged morning stiffness are suggestive of rheumatoid arthritis (RA). Patients with chronic rheumatologic diseases such as RA have high circulating levels of inflammatory cytokines, which can trigger **anemia of chronic disease** (ACD) due to maladaptive changes in iron utilization.

ACD is primarily mediated by **hepcidin**, a small peptide released by the liver in response to inflammation. Hepcidin binds to and inactivates iron channels (ferroportin) on enterocytes and reticuloendothelial macrophages, leading to reduced iron absorption in the gut and reduced iron recycling by the reticuloendothelial system (the site of senescent erythrocyte destruction and the source of >95% of daily iron for new RBC production). These changes significantly **reduce circulating iron levels**, which impairs the generation of heme for new erythrocytes. Although patients with suspected ACD do not generally require bone marrow biopsy for diagnosis, it would show **increased sequestration of iron within macrophages** and reduced quantities of erythrocyte precursor cells (eg, normoblasts, reticulocytes).

Patients with ACD typically develop a normocytic (or slightly microcytic) anemia with low reticulocyte count. Treatment of the underlying inflammatory condition (eg, methotrexate for RA) reduces serum inflammatory cytokine levels and generally improves the anemia.

(Choice B) In contrast to ACD, patients with iron deficiency anemia have reduced serum iron levels and reduced bone marrow iron levels due to low total body iron stores

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require bone marrow biopsy for diagnosis, it would show **increased sequestration of iron within macrophages** and reduced quantities of erythrocyte precursor cells (eg, normoblasts, reticulocytes).

Patients with ACD typically develop a normocytic (or slightly microcytic) anemia with low reticulocyte count. Treatment of the underlying inflammatory condition (eg, methotrexate for RA) reduces serum inflammatory cytokine levels and generally improves the anemia.

(Choice B) In contrast to ACD, patients with iron deficiency anemia have reduced serum iron levels and reduced bone marrow iron levels due to low total body iron stores.

Educational objective:

Anemia of chronic disease is caused by elevated inflammatory cytokine levels (eg, hepcidin), which increase sequestration of iron within the reticuloendothelial system and reduce circulating iron levels. Many patients have improvement in anemia with treatment of the underlying condition that caused the inflammation.

Pathophysiology	Hematology & Oncology	Anemia of inflammation
Subject	System	Topic

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order. Once you click **Proceed to Next Item**, you will not be able to add or change an answer.

A 24-year-old woman is being evaluated for chronic fatigue. She has a history of heavy menstrual periods since menarche and also recalls frequent nosebleeds as a child. Her past medical history is otherwise insignificant and she takes no medications. Laboratory studies show a hemoglobin level of 9.2 g/dL, a mean corpuscular volume of 72 fL, and decreased levels of ferritin.

Item 1 of 2

Which of the following is the most likely diagnosis?

A. Antiphospholipid syndrome (7%)
B. Factor VIII deficiency (10%)
C. Factor XIII deficiency (1%)
D. Immune thrombocytopenia (11%)
E. Protein C deficiency (3%)
F. von Willebrand factor deficiency (65%)

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Laboratory characteristics of coagulopathies

	PT	aPTT	Platelet count	Bleeding time
Hemophilia A & B	Normal	↑	Normal	Normal
von Willebrand factor deficiency	Normal	Normal or ↑	Normal	↑
Disseminated intravascular coagulation	↑	↑	↓	↑
Uremic platelet dysfunction	Normal	Normal	Normal	↑
Heparin administration	Normal	↑	Normal (except in heparin-induced thrombocytopenia)	Normal

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Disseminated intravascular coagulation	↑	↑	↓	↑
Uremic platelet dysfunction	Normal	Normal	Normal	↑
Heparin administration	Normal	↑	Normal (except in heparin-induced thrombocytopenia)	Normal
Warfarin use	↑	↑ (weak effect)	Normal	Normal
Immune thrombocytopenia	Normal	Normal	↓	↑

aPTT = activated partial thromboplastin time; PT = prothrombin time.

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This patient has microcytic anemia with a low ferritin level, which is characteristic of **iron deficiency anemia**. In developed countries, iron deficiency anemia is most commonly caused by overt or occult blood loss. The patient's history of heavy menstrual periods (**menorrhagia**) since menarche and frequent

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This patient has microcytic anemia with a low ferritin level, which is characteristic of **iron deficiency anemia**. In developed countries, iron deficiency anemia is most commonly caused by overt or occult blood loss. The patient's history of heavy menstrual periods (**menorrhagia**) since menarche and frequent nosebleeds (**epistaxis**) as a child further suggests **von Willebrand disease** (vWD) as the most likely etiology of her anemia.

In vWD, a mutation results in impaired synthesis in von Willebrand factor, leading to a qualitative defect in platelet binding and aggregation. As a result, patients with vWD experience easy bleeding from **skin and mucosal sites**, including the gingivae, nasal mucosa, gastrointestinal tract, and endometrium.

(Choice A) Antiphospholipid syndrome causes a hypercoagulable state that increases the risk of thromboses and spontaneous abortion.

(Choice B) Factor VIII deficiency causes hemophilia A. Severe forms of vWD can also result in factor VIII deficiency as factor VIII is protected from degradation by vWF. However, this patient does not have the characteristic deep-tissue bleeding (eg, bleeding into joints/muscles, gastrointestinal bleeding, hematuria) typically seen with clotting factor deficiencies.

(Choice C) Factor XIII deficiency is an extremely rare autosomal recessive disorder that causes clot instability. Affected patients often have delayed, recurrent bleeding after trauma or surgery. Hemophilia-

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characteristic deep-tissue bleeding (eg, bleeding into joints/muscles, gastrointestinal bleeding, hematuria) typically seen with clotting factor deficiencies.

(Choice C) Factor XIII deficiency is an extremely rare autosomal recessive disorder that causes clot instability. Affected patients often have delayed, recurrent bleeding after trauma or surgery. Hemophilia-like bleeding (eg, deep-tissue bleeding) is seen in factor XIII deficiency.

(Choice D) Immune thrombocytopenia (formerly immune thrombocytopenic purpura) produces isolated thrombocytopenia with episodic bleeding that is typically mucocutaneous (eg, petechiae, purpura, epistaxis). However, the associated bleeding is unlikely to be chronic and unrelenting since childhood.

(Choice E) Protein C is a natural anticoagulant protein, and deficiency results in a procoagulant state that most commonly manifests with recurrent deep venous thromboses.

Educational objective:
Patients with von Willebrand disease often present with a lifelong history of mucosal bleeding, including gingival bleeding, epistaxis, and/or menorrhagia. These patients have normal platelet levels but typically have a prolonged bleeding time due to impaired platelet functioning.

Pathophysiology Hematology & Oncology Von willebrand disease

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Item 2 of 2

Further evaluation shows decreased von Willebrand factor activity in the patient's serum. This protein normally binds to which of the following?

- A. Collagen (74%)
- B. Fibrin polymer (11%)
- C. Prostacyclin (1%)
- D. Protein C (3%)
- E. Thrombin (8%)

Correct

74% Answered correctly

22 secs Time Spent

12/18/2020 Last Updated

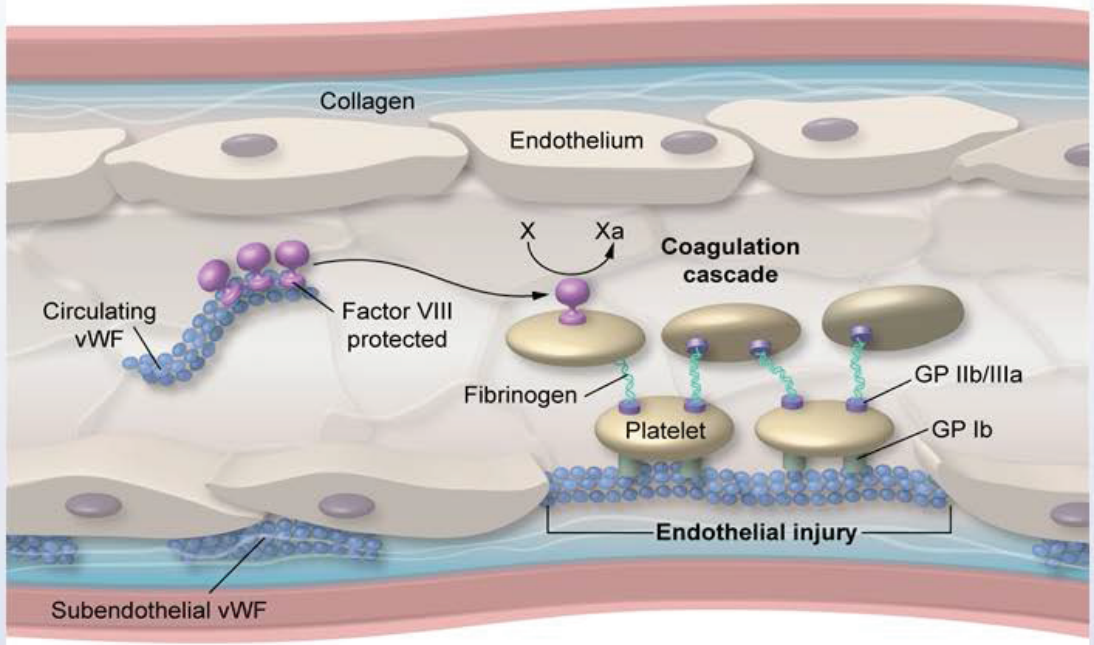
Explanation

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Explanation

Platelet adhesion & activation via von Willebrand factor



GP = glycoprotein; **vWF** = von Willebrand factor.

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GP = glycoprotein; vWF = von Willebrand factor.

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von Willebrand factor (vWF) serves 2 important roles in hemostasis:

1. vWF promotes **platelet adhesion** at sites of vascular injury by binding to and crosslinking **platelet glycoproteins** (primarily GpIb) with **exposed collagen** underneath damaged endothelium. vWF also enhances platelet aggregation, particularly under conditions of high shear stress (such as in small vessels).
2. vWF functions as a protective **carrier protein for factor VIII** that increases its plasma half-life. In the absence of vWF, factor VIII is rapidly degraded in the circulation via proteolytic inactivation.

(Choice B) A hemostatic fibrin polymer is the end result of the coagulation cascade. Fibrin also plays a role in inflammation and coagulation regulation.

(Choice C) Prostacyclin functions both as an inhibitor of platelet aggregation and a vasodilator.

(Choice D) Protein C is a vitamin K-dependent anticoagulant activated by bound thrombin in the presence of endothelial thrombomodulin. Protein C acts together with protein S to inactivate the activated forms of factors V and VIII, which are necessary for the production of thrombin.

(Choice E) Thrombin is produced from prothrombin by activated factor X. Thrombin, in turn, converts fibrinogen to fibrin. Thrombin also activates factors V, VIII, and XIII.

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(Choice B) A hemostatic fibrin polymer is the end result of the coagulation cascade. Fibrin also plays a role in inflammation and coagulation regulation.

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(Choice E) Thrombin is produced from prothrombin by activated factor X. Thrombin, in turn, converts fibrinogen to fibrin. Thrombin also activates factors V, VIII, and XIII.

Educational objective:

von Willebrand factor (vWF) functions as a promoter of platelet adhesion at sites of vascular injury by binding platelet glycoproteins to subendothelial collagen on injured blood vessel walls. It also acts as a protective carrier protein for circulating factor VIII.

References

- Platelet adhesive dynamics. Part II: high shear-induced transient aggregation via GPIba-vWF-GPIba bridging.

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www.ncbi.nlm.nih.gov/pubmed/18515386

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A 5-year-old boy is brought to the emergency department due to an hour of epistaxis after he was elbowed in the face during a basketball game. He has a history of prolonged bleeding from the gums after brushing his teeth. Vital signs are normal. The patient has scattered bruises along his arms and legs. He receives desmopressin, which stops the bleeding. This treatment most likely improved the patient's condition through which of the following therapeutic mechanisms?

A. ~~Binds to antidiuretic hormone receptors~~ (6%)

B. ~~Increases circulating factor IX~~ (2%)

C. Increases circulating von Willebrand factor (84%)

D. ~~Increases platelet count~~ (1%)

E. ~~Increases vitamin K–dependent coagulation factors~~ (2%)

F. ~~Relaxes vascular smooth muscle cells~~ (1%)

Correct

84% Answered correctly

43 secs Time Spent

12/03/2020 Last Updated

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www.ncbi.nlm.nih.gov/pubmed/18515386

Effects of desmopressin (DDAVP) therapy	
Mild hemophilia A & Type 1 von Willebrand disease	Increases circulating factor VIII & endothelial secretion of vWF to stop bleeding
Central diabetes insipidus & Nocturnal enuresis	Binds to V2 receptors in renal tubular cells, leading to increased aquaporin channels, increased water reabsorption & decreased urine output

vWF = von Willebrand factor.

This patient's history of prolonged mucosal bleeding (eg, oropharyngeal, nasal), easy bruising, and responsiveness to desmopressin (DDAVP) likely indicate **von Willebrand disease** (vWD), the most common inherited bleeding disorder. VWD is caused by qualitative or quantitative defect in von Willebrand factor (vWF), a multimeric glycoprotein synthesized by endothelial cells and platelets. VWF contributes to hemostasis by forming a bridge between platelets and exposed subendothelial components at sites of injury and by serving as a carrier protein for factor VIII (whose half-life is tremendously shortened when not

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factor (vWF), a multimeric glycoprotein synthesized by endothelial cells and platelets. VWF contributes to hemostasis by forming a bridge between platelets and exposed subendothelial components at sites of injury and by serving as a carrier protein for factor VIII (whose half-life is tremendously shortened when not bound to vWF).

Treatment of minor bleeding episodes in patients with vWD often involves **desmopressin** (DDAVP), a synthetic analogue of antidiuretic hormone that does not induce vasoconstriction. DDAVP induces a rapid and transient **increase in vWF** and factor VIII by indirectly releasing these compounds from **endothelial storage sites**. DDAVP is most useful in the acute setting, as repeated doses have limited effectiveness due to tachyphylaxis (endothelial stores become depleted).

(Choices A and F) Antidiuretic hormone binds to the vasopressin 2 receptor on renal tubular cells, which leads to increased aquaporin channels, increased water reabsorption, and decreased urine output. It also binds to the vasopressin 1 (V1) receptor on vascular smooth muscle, which results in vasoconstriction. In contrast, DDAVP has antidiuretic effects but little or no vasoactive (vasoconstrictive) effects because it only binds to the V2 receptor.

(Choice B) Factor IX, a vitamin K–dependent clotting factor produced in the liver, is deficient in hemophilia B. DDAVP has no effect on factor IX levels. Hemophilia B must be treated with factor IX replacement.

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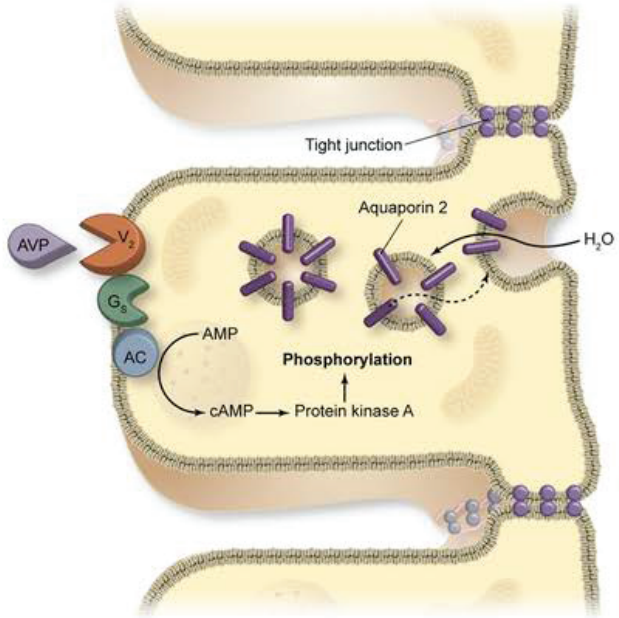
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factor (vWF), a multimeric glycoprotein synthesized by endothelial cells and platelets. VWF contributes to

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ADH action on collecting duct



AC = adenylyl cyclase; **ADH** = antidiuretic hormone; **AVP** = arginine vasopressin; **cAMP** = cyclic AMP.
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www.ncbi.nlm.nih.gov/pubmed/18515386

contrast, DDAVP has antidiuretic effects but little or no vasoactive (vasoconstrictive) effects because it only binds to the V2 receptor.

(Choice B) Factor IX, a vitamin K–dependent clotting factor produced in the liver, is deficient in hemophilia B. DDAVP has no effect on factor IX levels. Hemophilia B must be treated with factor IX replacement.

(Choice D) Platelets form the initial hemostatic plug when bleeding occurs. DDAVP has no effect on platelet number.

(Choice E) Patients with vitamin K deficiency are prone to bleeding due to decreased vitamin K–dependent coagulation factors (factors II, VII, IX, and X). Vitamin K deficiency is typically seen in patients with fat malabsorption (eg, pancreatic insufficiency) or those on warfarin, a vitamin K antagonist.

Educational objective:

Patients with symptomatic von Willebrand disease can be treated with desmopressin (DDAVP), a synthetic antidiuretic hormone analogue that has no vasoconstrictive effects. DDAVP transiently increases von Willebrand factor and factor VIII release from endothelial cell storage through indirect mechanisms; it can be used prophylactically prior to procedures or to treat minor bleeding.

References

- Desmopressin (DDAVP) in the treatment of bleeding disorders: the first 20 years

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A 66-year-old woman is brought to the emergency department due to left leg pain. Five days ago, the patient underwent elective right hip arthroplasty for advanced osteoarthritis. She had been recovering well at an acute rehabilitation facility until she woke today with severe left calf pain and swelling. The patient has taken daily subcutaneous, low-molecular-weight heparin and as-needed acetaminophen since the surgery. She has no other medical conditions. Temperature is 37 C (98.6 F), blood pressure is 130/70 mm Hg, and pulse is 92/min. The surgical incision over her right hip is healing well. Her left posterior calf is tender and swollen to the knee. Three days ago, complete blood count was normal, but platelet count is now 70,000/mm^3. Peripheral blood smear shows decreased platelet number but no other abnormalities. Which of the following is the most likely cause of this patient's thrombocytopenia?

A. ~~Decreased bone marrow platelet production~~ (2%)

B. ~~Mechanical destruction of platelets~~ (9%)

C. Non–immune-mediated platelet clumping (40%)

✓ D. Platelet removal by splenic macrophages (26%)

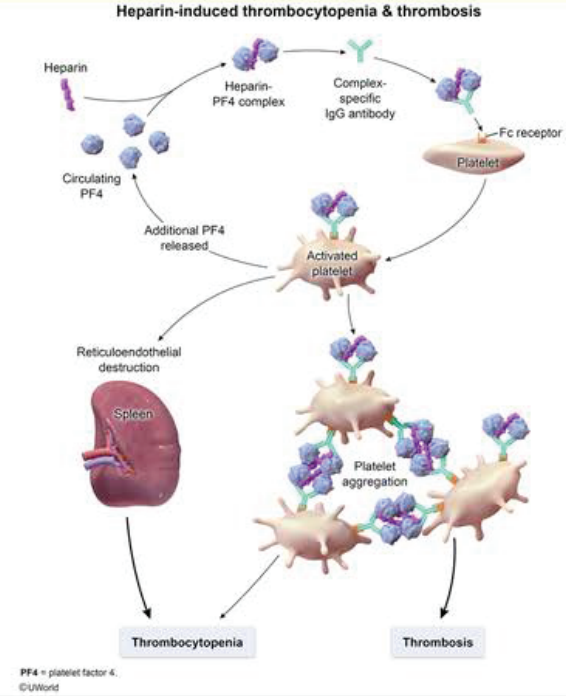
E. ~~Uncontrolled activation of the coagulation cascade~~ (19%)

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PF4 = platelet factor 4.

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This patient on low-molecular-weight heparin developed thrombocytopenia and deep venous thrombosis (calf pain/swelling), raising strong suspicion for heparin-induced thrombocytopenia **(HIT) type 2**. In HIT type 2, heparin induces a conformational change in platelet-factor 4, leading to the formation of a neoantigen. **IgG antibodies** form against the neoantigen (**heparin-platelet factor 4**), which results in antibody aggregation on the platelet surface.

Patients generally develop manifestations **5-10 days** after heparin initiation. **Thrombocytopenia** is the hallmark feature due to the clearance of antibody-coated platelets by **splenic macrophages**. Antibody aggregation on the platelet surface also results in wide-spread platelet aggregation, which worsens the thrombocytopenia and significantly increases the risk of **venous and arterial thrombosis**.

Patients with HIT-type 2 should immediately stop heparin and be initiated on a **nonheparin anticoagulant** (eg, argatroban) to help prevent/treat thrombosis.

(Choice A) Although bone marrow suppression can cause thrombocytopenia, it most often occurs in the setting of malignant invasion of the bone marrow (eg, leukemia) or chemical toxicity (eg, chemotherapy, excessive alcohol). Thrombosis is uncommon.

(Choices B and E) Mechanical destruction of platelets can be seen with a mechanical prosthetic heart

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setting of malignant invasion of the bone marrow (eg, leukemia) or chemical toxicity (eg, chemotherapy, excessive alcohol). Thrombosis is uncommon.

(Choices B and E) Mechanical destruction of platelets can be seen with a mechanical prosthetic heart valve or in disseminated intravascular coagulation, a condition marked by the excessive activation of the coagulation cascade. In both of these conditions, thrombocytopenia is accompanied by schistocytes on peripheral blood smear.

(Choice C) HIT type 1 is a non–immune-mediated condition caused by platelet clumping. Thrombocytopenia is typically mild (nadir ~100,000/mm^3), and most cases arise within 2 days of heparin administration. It does not cause thrombosis and is not considered clinically significant; therefore, heparin can be continued.

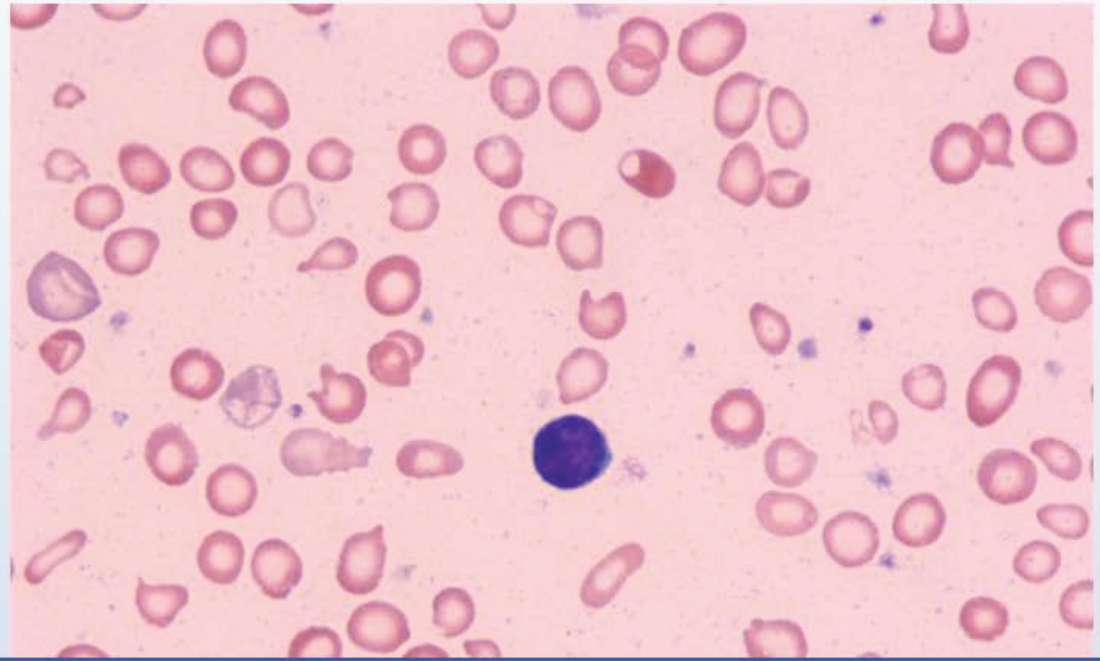
Educational objective:
Heparin-induced thrombocytopenia type 2 results from the formation of IgG antibodies to complexes of heparin and endogenous platelet factor 4. The major manifestation is thrombocytopenia, which typically occurs 5-10 days after heparin initiation due to the destruction of antibody-coated platelets by splenic macrophages. Widespread intravascular platelet activation also results in a high risk of arterial and venous thrombosis.

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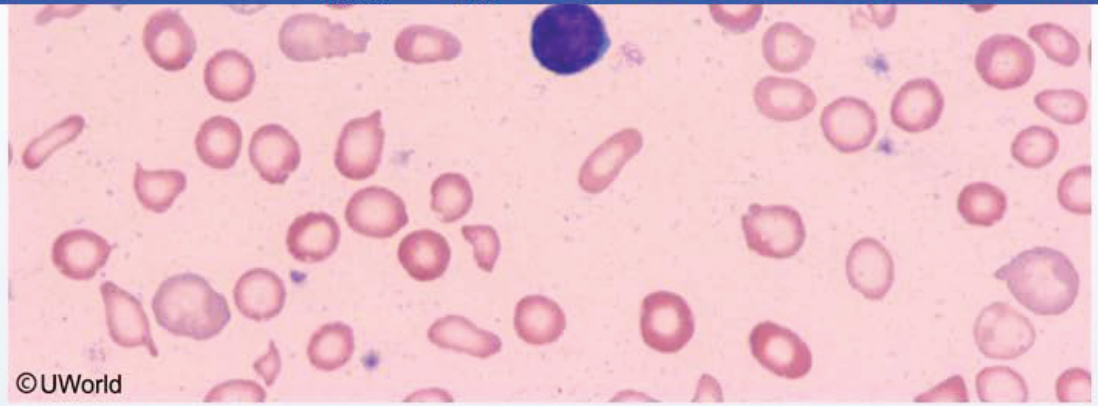
A 19-year-old woman comes to the office due to exertional dyspnea and intermittent lightheadedness. On examination, mucosal pallor is present. Laboratory studies reveal a red blood cell count of 3.5 million/mm^3 and a hemoglobin concentration of 8.5 g/dL. Peripheral smear is shown in the image below:



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Which of the following findings are most likely present in this patient?

A. Decreased transferrin binding capacity (12%)

B. ~~Increased macrophage iron retention~~ (9%)

C. Increased serum cytokine levels (6%)

D. Increased serum erythropoietin levels (56%)

E. Increased serum hepcidin levels (14%)

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	Iron deficiency anemia	Anemia of chronic disease
Serum ferritin	↓	Normal or ↑
Serum iron	↓	↓
Mean corpuscular volume	↓	Normal or ↓
Transferrin (total iron-binding capacity)	↑	Normal or ↓
Transferrin saturation	↓	↓
Erythropoietin	↑	Variable*
Hepcidin	↓	↑
C-reactive protein	Normal	↑
Serum cytokines	Normal	↑

* Lower than expected for the degree of anemia.

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This patient's dyspnea, lightheadedness, and mucosal pallor are likely due to **symptomatic anemia**. A number of underlying processes can cause anemia, but the differential diagnosis can usually be narrowed by concurrent clinical data. In this case, the peripheral blood smear demonstrates **hypochromic, microcytic erythrocytes** and a variety of erythrocyte shapes **(poikilocytosis)**, raising strong suspicion for severe iron deficiency anemia (IDA). Young women often develop IDA from heavy menstruation.

Patients with severe IDA do not have enough iron to generate adequate hemoglobin for each erythrocyte, which results in low mean corpuscular hemoglobin concentration (hypochromia) and small erythrocyte size (microcytosis). Interstitial fibroblasts in the peritubular capillaries and proximal convoluted tubule of the kidney detect the reduced oxygen carrying capacity of the blood (mild tissue hypoxia) and **increase erythropoietin release** to drive the generation of new erythrocytes. However, new erythrocytes cannot be produced at a level to compensate for the anemia due to insufficient serum iron; therefore, patients typically have **minimal reticulocytes** and **low red blood cell counts** in the peripheral blood.

(Choice A) Transferrin is a serum protein that binds free iron. The concentration of transferrin is increased in IDA (to maximize free iron scavenge), but the amount of iron bound to it is reduced, leading to a low transferrin saturation on laboratory evaluation.

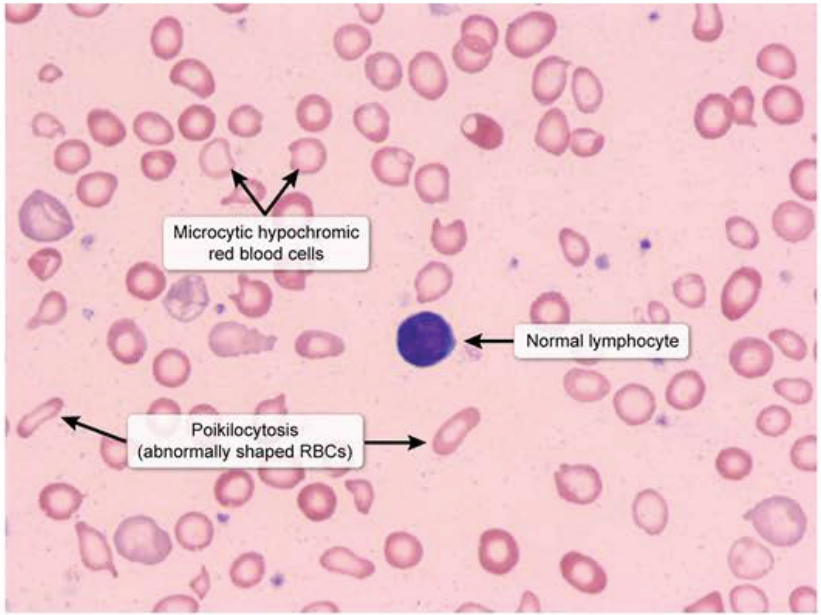
(Choices B, C, and E) Hepcidin is a small peptide released by the liver in response to inflammation. It

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Iron deficiency anemia



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(Choices B, C, and E) Hepcidin is a small peptide released by the liver in response to inflammation. It

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(Choices B, C, and E) Hepcidin is a small peptide released by the liver in response to inflammation. It binds to and inhibits iron channels on the surface of enterocytes and on reticuloendothelial macrophages, which reduces iron absorption in the gut and reduces iron release from the reticuloendothelial system (the primary site of iron recycling). Because IDA is not mediated by inflammation, hepcidin levels are typically low; this increases gastrointestinal iron absorption and iron release from the reticuloendothelial system (eg, splenic macrophages). In contrast, anemia of chronic disease is associated with very high levels of hepcidin (and other inflammatory cytokines), which reduces iron availability for erythrocytosis despite adequate total body stores of iron. Patients with anemia of chronic disease typically have normocytic anemia and normochromia (not hypochromia).

Educational objective:

Patients with severe iron deficiency anemia (IDA) typically have evidence of hypochromic, microcytic erythrocytes on peripheral blood smear with poikilocytosis. Laboratory studies will reveal low red blood cell count, low hepcidin, and high transferrin. Although erythropoietin is markedly elevated in IDA, there is not enough iron to efficiently generate erythrocytes; therefore, reticulocyte count is low.

Pathophysiology	Hematology & Oncology	Iron deficiency anemia
Subject	System	Topic

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A 48-year-old woman comes to the emergency department with headache, dizziness, and nausea for the past several hours. She has no fever, nasal congestion, or cough but reports that her husband has also been complaining of headache. The patient has been burning wood in the fireplace to warm her house after losing electricity during a snowstorm. Her temperature is 37 C (98.6 F), blood pressure is 135/70 mm Hg, and pulse is 94/min and regular. Physical examination is unremarkable. The substance responsible for this patient's condition most likely impairs hemoglobin function through which of the following mechanisms?

A. Alteration of the partial pressure of oxygen (1%)
B. Competitive binding to heme (86%)
C. Deactivation of a reductase enzyme (1%)
D. Denaturation of the globin chains (0%)
E. Irreversible linking to heme (9%)
F. Oxidation of the porphyrin ring (0%)

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This patient most likely has **carbon monoxide (CO) poisoning**, a condition that presents with nonspecific findings ranging from headache and dizziness to convulsions and respiratory arrest depending on concentration and exposure. CO is a colorless, odorless, tasteless gas that is a byproduct of incomplete hydrocarbon combustion. CO poisoning is most often caused by smoke inhalation from a fire or the burning of fuel sources such as wood, coal, or natural gas in poorly ventilated environments.

CO toxicity occurs because of CO's ability to competitively bind iron present in heme proteins. The gas binds to heme iron with a much higher affinity than oxygen, forming **carboxyhemoglobin**. Even if only 1 of the 4 heme sites is affected, the remaining 3 heme groups have **increased oxygen affinity** (leftward shift of the oxygen dissociation curve), impeding oxygen delivery to tissues. CO is also capable of binding cardiac myoglobin with high affinity, disrupting the heart's ability to use oxygen and thereby decreasing cardiac output. At a cellular level, CO binds to cytochrome oxidase, inhibiting aerobic metabolism and exacerbating tissue hypoxia.

Treatment for CO poisoning is administration of **high-flow or hyperbaric oxygen** therapy as this hastens the dissociation of CO from carboxyhemoglobin.

(Choice A) The partial pressure of oxygen (pO_2) is a measure of dissolved oxygen in the plasma, the amount of which does not change in CO poisoning.

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the dissociation of CO from carboxyhemoglobin.

(Choice A) The partial pressure of oxygen (pO_2) is a measure of dissolved oxygen in the plasma, the amount of which does not change in CO poisoning.

(Choice C) NADH methemoglobin reductase reduces ferric iron (Fe^{3+}) to ferrous iron (Fe^{2+}), regenerating hemoglobin from methemoglobin. Enzyme deficiency results in congenital methemoglobinemia.

(Choice D) Globin chain denaturation occurs in G6PD-deficient red blood cells when oxidant stressors cause sulfhydryl group cross-linking.

(Choice E) CO reversibly binds hemoglobin at its heme moieties.

(Choice F) Heme consists of an iron bound to protoporphyrin IX. CO binds to iron in metalloproteins but does not cause oxidation of the porphyrin component.

Educational objective:
Carbon monoxide binds heme iron in hemoglobin with an affinity much greater than oxygen, generating carboxyhemoglobin. Remaining binding sites on carboxyhemoglobin have an increased affinity for oxygen that causes the oxygen dissociation curve to shift to the left, impeding oxygen delivery to tissues.

References

- Carbon monoxide intoxication

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A 56-year-old man comes to the emergency department due to right lower extremity pain and swelling. The symptoms began shortly after he flew back to the United States from a 7-day cruise in Indonesia. Doppler ultrasonography reveals a femoropopliteal venous thrombosis, and the patient is given anticoagulation with rivaroxaban. Compared to vitamin K antagonists, this patient's treatment is most likely to have which of the following benefits?

A. Better patient compliance (9%)
B. Greater efficacy (6%)
C. Less risk of thrombocytopenia (11%)
D. No need for loading dose (15%)
✓ E. Less variability in therapeutic effect (56%)

Correct

56%
Answered correctly

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10/12/2020
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Direct oral anticoagulants (DOACs) versus warfarin		
	DOACs	**Warfarin**
Dosing	>1 dose daily may be required	Once daily
Dietary restrictions	None	Stable vitamin K intake required
Drug interactions	Few	Many
Required monitoring	None	INR
Comorbid conditions	Renal failure may prohibit use	No prohibitions

Rivaroxaban is a direct oral anticoagulant (DOAC) that binds to and **inhibits factor Xa**, thereby preventing conversion of prothrombin to thrombin. DOACs are generally preferred over vitamin K antagonists (VKAs) such as warfarin for most conditions requiring prolonged anticoagulation due to **less variability in therapeutic effect**.

The therapeutic effect of VKAs is affected by changes to dietary intake of vitamin K, disruption to vitamin K– producing intestinal flora (eg, antibiotics), and a wide range of medications that inhibit or induce

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therapeutic effect.

The therapeutic effect of VKAs is affected by changes to dietary intake of vitamin K, disruption to vitamin K– producing intestinal flora (eg, antibiotics), and a wide range of medications that inhibit or induce cytochrome P450 2C9; therefore, patients given VKAs require coagulation monitoring (eg, with INR) to ensure adequate anticoagulation. In contrast, the therapeutic effect of DOACs is not typically altered by environmental or medication changes; therefore, **laboratory monitoring is not required**. DOACs may also have a lower risk of intracranial bleeding, the most serious risk of anticoagulation, when compared to VKAs.

(Choice A) Rates of patient compliance are roughly equivalent for DOACs and VKAs.

(Choices B and C) Heparin can cause thrombocytopenia due to either heparin-induced thrombocytopenia type I (nonimmune mediated) or type 2 (immune mediated). VKAs target vitamin K–dependent clotting factors (not platelets), so they do not typically cause thrombocytopenia. VKAs and DOACs have roughly the same efficacy.

(Choice D) A loading dose is required with heparin. Some DOACs (eg, rivaroxaban) also require a higher dose for the first few weeks prior to initiating a lower maintenance dose. VKAs do not require a loading dose.

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(Choices B and C) Heparin can cause thrombocytopenia due to either heparin-induced thrombocytopenia type I (nonimmune mediated) or type 2 (immune mediated). VKAs target vitamin K–dependent clotting factors (not platelets), so they do not typically cause thrombocytopenia. VKAs and DOACs have roughly the same efficacy.

(Choice D) A loading dose is required with heparin. Some DOACs (eg, rivaroxaban) also require a higher dose for the first few weeks prior to initiating a lower maintenance dose. VKAs do not require a loading dose.

Educational objective:
Direct oral anticoagulants (DOACs) such as rivaroxaban are often preferred over vitamin K antagonists (VKAs) such as warfarin in the treatment of conditions that require anticoagulation due to less variability in therapeutic drug effect; in contrast to VKAs, the efficacy of DOACs is unaffected by dietary changes and most medications. Therefore, patients given DOACs do not require laboratory monitoring.

Pharmacology	Hematology & Oncology	Anticoagulants
Subject	System	Topic

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A 62-year-old woman comes to the office due to a month of progressive right chest and back pain. The patient also noticed a right breast lump several months ago, which has grown over time. She has no prior medical issues, has not seen a physician for many years, and has had no cancer screenings. Physical examination reveals a hard, 5-cm right breast mass, enlarged axillary lymph nodes, and point tenderness along the right-sided ribs and 10th thoracic vertebra. Biopsy of the breast mass shows hormone receptor–positive, HER2-negative, invasive ductal carcinoma. Skeletal survey demonstrates lytic lesions of the ribs and thoracic vertebrae. As part of the treatment regimen, the patient receives a medication that is a potent inhibitor of cyclin-dependent kinase. Which of the following is the most likely dose-limiting toxicity of this medication?

- A. Bone marrow suppression (65%)
- B. Cardiomyopathy (18%)
- C. Immune-mediated toxicity (5%)
- D. Peripheral neuropathy (6%)
- E. Sensorineural hearing loss (4%)

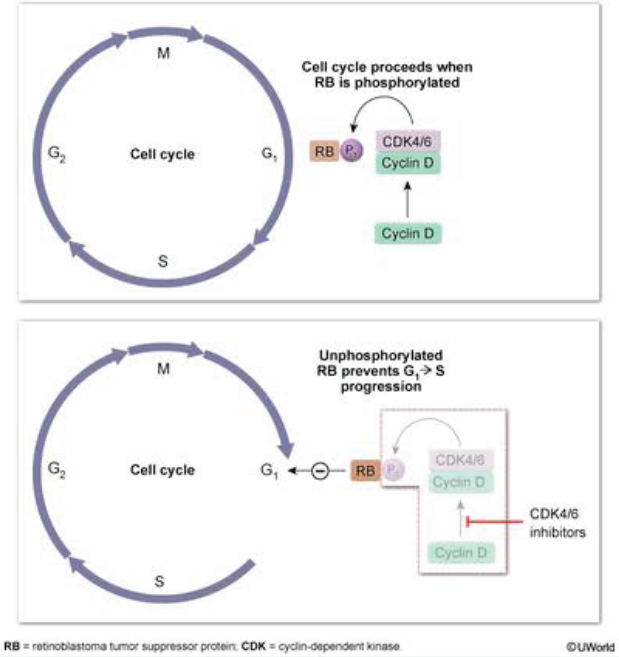
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CDK4/6 inhibitors



RB = retinoblastoma tumor suppressor protein; CDK = cyclin-dependent kinase.

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RB = retinoblastoma tumor suppressor protein; **CDK** = cyclin-dependent kinase.

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The cellular growth cycle consists of 4 distinct phases: G_1, S, G_2, and M. Progression through the phases is controlled by surveillance systems (checkpoints) that interrupt the cell cycle and/or induce apoptosis if cells do not meet the requirements to progress forward:

- The transition from $G_1 \rightarrow S$ (initiation of DNA replication) is controlled by a combination of cell size and nutrient status, exposure to growth factors, and proper surveillance and repair of damaged DNA.
- At the $G_2 \rightarrow M$ transition, the cell again checks for DNA damage and repairs replication errors before they can be passed on to daughter cells during mitosis. An additional spindle checkpoint ensures that duplicated chromosomes separate appropriately during cell division.

Cyclin-dependent kinases (CDKs) 4 and 6 control cell cycle progression from $G_1 \rightarrow S$. These CDKs are activated by cyclin D and subsequently inhibit the retinoblastoma tumor suppressor protein, leading to the upregulation of transcriptional factors that **progress the cell cycle** to S phase. Many cancers exploit this crucial checkpoint and achieve unregulated cellular growth via cyclin D amplification (or inactivating mutations to *retinoblastoma* gene).

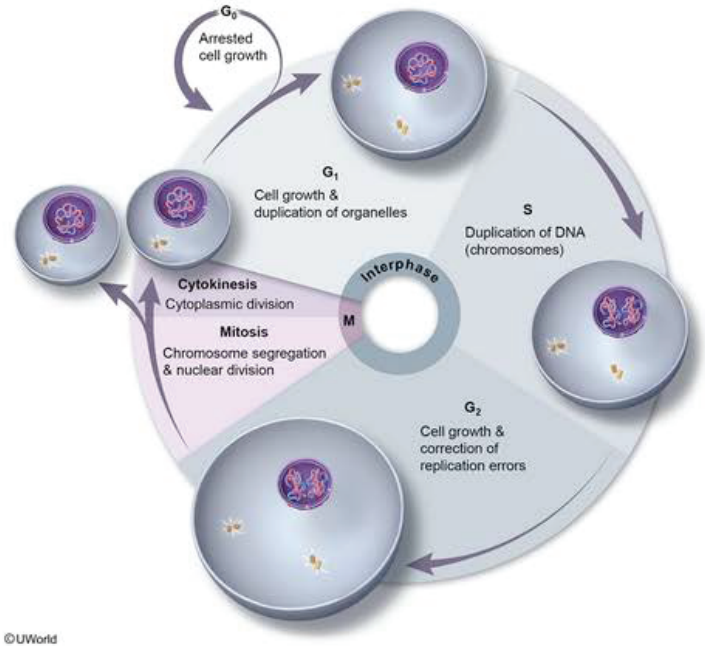
CDK 4/6 inhibitors (eg, palbociclib) can be used to block the cyclin D binding site on CDK, which results in

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Phases of the cell cycle



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Cyclin-dependent kinases (CDKs) 4 and 6 control cell cycle progression from $G_1 \rightarrow S$. These CDKs are activated by cyclin D and subsequently inhibit the retinoblastoma tumor suppressor protein, leading to the upregulation of transcriptional factors that **progress the cell cycle** to S phase. Many cancers exploit this crucial checkpoint and achieve unregulated cellular growth via cyclin D amplification (or inactivating mutations to *retinoblastoma* gene).

CDK 4/6 inhibitors (eg, palbociclib) can be used to block the cyclin D binding site on CDK, which results in decreased CDK 4/6 activation, increased activity of the retinoblastoma tumor suppressor protein, and cell cycle arrest. Although CDK 4/6 inhibitors are generally well tolerated, they often **inhibit** cellular replication in other **rapidly dividing cells**, particularly hematologic cells in the **bone marrow**. This can result in treatment-limiting hematologic side effects such as neutropenia, leukopenia, and anemia.

(Choice C) Immunotherapy that targets PD-1, PD-L1, and CTLA-4 enhances the immune response against cancer and is often used in the treatment of malignant melanoma. The major side effects of these medications are autoimmune-related adverse events, including skin, liver, gastrointestinal, and endocrine inflammation.

(Choices B, D, and E) CDK 4/6 inhibitors do not generally cause adverse side effects in cells that are arrested in G_0, such as myocytes, cochlear hair cells, or neurons. Cardiomyopathy is a common side effect

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against cancer and is often used in the treatment of malignant melanoma. The major side effects of these medications are autoimmune-related adverse events, including skin, liver, gastrointestinal, and endocrine inflammation.

(Choices B, D, and E) CDK 4/6 inhibitors do not generally cause adverse side effects in cells that are arrested in G_0, such as myocytes, cochlear hair cells, or neurons. Cardiomyopathy is a common side effect of anthracyclines (eg, doxorubicin) and HER2 antibodies (eg, trastuzumab). Sensorineural hearing loss can be seen with platinum-based chemotherapy (eg, cisplatin). Peripheral neuropathy is a common side effect of vincristine and bortezomib.

Educational objective:

Cyclin-dependent kinases (CDKs) 4/6 regulate the movement of cells from $G_1 \rightarrow S$ phase. Cancers often have mutations that enhance the activity or downstream effects of CDK 4/6, which contribute to unregulated cellular growth. Inhibitors to CDK 4/6 can be used to treat certain forms of cancer. However, they can inhibit cellular replication in other rapidly dividing cells such as the hematologic cells in the bone marrow (eg, neutropenia, anemia, or thrombocytopenia).

References

- Palbociclib in hormone-receptor-positive advanced breast cancer.

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A 35-year-old woman comes to the hospital due to sudden-onset numbness in her left arm and face. The patient has had generalized headache, dyspnea on exertion, and easy fatigability for several days but no weakness. She has a history of well-controlled asthma. Temperature is 37.7 C (99.9 F), blood pressure is 110/60 mm Hg, and pulse is 80/min. Light touch sensation is decreased in the left upper extremity and the lower left side of the face. Strength and reflexes are normal. Cardiopulmonary and abdominal examinations are unremarkable. There is no skin rash. Laboratory results are as follows:

Hemoglobin	8.6 g/dL
Platelets	24,000/mm^3
Blood urea nitrogen	32 mg/dL
Creatinine	1.9 mg/dL

PT and PTT are normal. Peripheral blood smear shows numerous schistocytes. Urinalysis is positive for mild proteinuria. Which of the following is the most likely underlying cause of this patient's current condition?

A. IgA immune complex deposition (14%)

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PT and PTT are normal. Peripheral blood smear shows numerous schistocytes. Urinalysis is positive for mild proteinuria. Which of the following is the most likely underlying cause of this patient's current condition?

A. IgA immune complex deposition (14%)
B. Impaired cleavage of von Willebrand factor (57%)
C. Plasma cell proliferation (4%)
D. Rupture of atheromatous plaque (8%)
E. Systemic coagulation factor activation (15%)

Correct

57%
Answered correctly

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Explanation

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Thrombotic thrombocytopenic purpura	
Pathophysiology	• ↓ ADAMTS-13 level → uncleaved vWF multimers → platelet trapping & activation • Acquired (autoantibody) or hereditary
Clinical features	• Hemolytic anemia (↑ LDH, ↓ haptoglobin) with schistocytes on peripheral smear • Thrombocytopenia (↑ bleeding time, normal PT/PTT) • Sometimes with: ◦ Renal failure ◦ Neurologic manifestations ◦ Fever

LDH = lactate dehydrogenase; **vWF** = von Willebrand factor.

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LDH = lactate dehydrogenase; **vWF** = von Willebrand factor.

This patient's severe **thrombocytopenia** and **schistocytes** on peripheral blood smear indicate **microangiopathic hemolytic anemia** (MAHA). The presence of **normal coagulation studies** indicate that there is no systemic activation of the coagulation cascade, which makes disseminated intravascular coagulation unlikely **(Choice E)**. Therefore, a platelet-activated thrombotic microangiopathy such as **thrombotic thrombocytopenic purpura** (TTP) or hemolytic uremic syndrome is most likely.

In this case, the patient has 4 of the 5 classic findings of acquired TTP:

- Severe thrombocytopenia, which may cause bruising or bleeding
- MAHA, which may cause symptomatic anemia (eg, fatigue, dyspnea on exertion)
- **Renal damage**, which may cause **renal insufficiency** (eg, elevated creatinine) and mild **proteinuria**
- **Neurologic damage**, which may cause confusion, **headache**, and **transient focal findings** (eg, numbness, weakness)
- Fever (not present)

Although this pentad of findings is classic, all 5 manifestations are rarely seen. In addition, a purpuric rash (due to subcutaneous bleeding) is sometimes, but not always, present.

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- Fever (not present)

Although this pentad of findings is classic, all 5 manifestations are rarely seen. In addition, a purpuric rash (due to subcutaneous bleeding) is sometimes, but not always, present.

Acquired TTP occurs due to the formation of an autoantibody inhibitor against **ADAMTS-13**, a von Willebrand factor (vWF)–cleaving protease. Circulating vWF (produced by megakaryocytes and endothelial cells) normally is released as large vWF multimers that are cleaved to their regular size by ADAMTS-13. These vWF multimers support hemostasis by bridging platelets and subendothelial components to sites of vascular injury. In TTP, the large **uncleaved vWF multimers** are significantly more prothrombotic and result in diffuse **microvascular thrombosis**.

(Choice A) Henoch-Schönlein purpura (IgA vasculitis) is characterized by IgA immune complex deposition. Typical manifestations include palpable purpura, renal disease, and arthritis/arthralgias. Platelet counts are usually normal.

(Choice C) Some features of this patient's presentation could be explained by plasma cell dyscrasias such as multiple myeloma (renal failure, anemia due to bone marrow replacement) and Waldenström macroglobulinemia (neurologic symptoms due to hyperviscosity, autoimmune hemolytic anemia). However, microangiopathic hemolytic anemia would be atypical.

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(Choice D) A cerebrovascular accident caused by plaque rupture could cause neurologic deficits but would not account for the patient's hematologic and renal abnormalities.

Educational objective:
Thrombotic thrombocytopenic purpura frequently results from impaired function of the von Willebrand factor (vWF)–cleaving protease ADAMTS-13, which causes the accumulation of uncleaved vWF multimers that are significantly more prothrombotic. Patients develop diffuse microvascular thrombosis, which leads to thrombocytopenia and microangiopathic hemolytic anemia.

References

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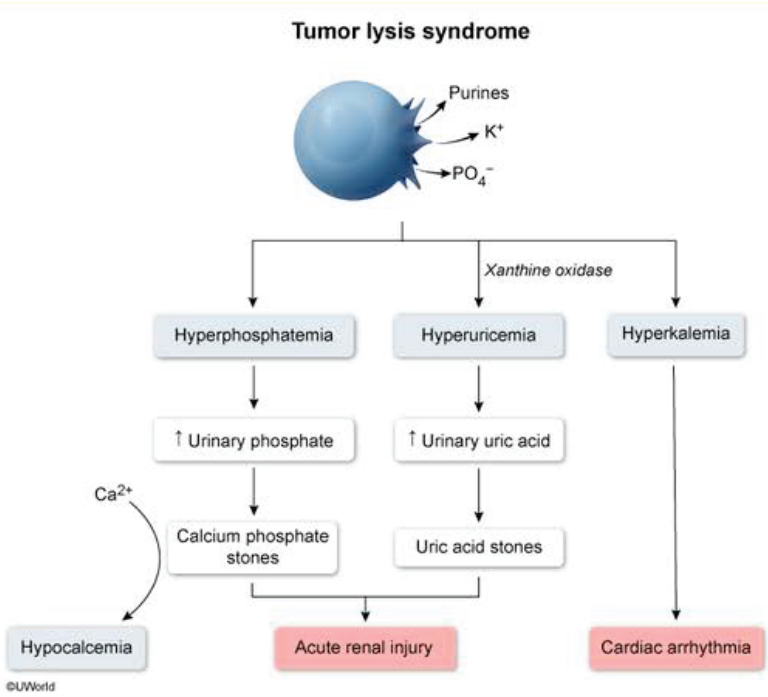
Down syndrome but has otherwise been healthy. Abdominal examination reveals the liver edge 3 cm below the costal margin and the spleen tip extending past the level of the umbilicus. Leukocyte count is 104,000/mm^3, and subsequent peripheral blood smear reveals numerous lymphoblasts. The patient is diagnosed with acute lymphoblastic leukemia and combination cytotoxic chemotherapy is planned. Which of the following laboratory changes are most likely to be seen in this patient following treatment initiation?

	Potassium	Uric acid	Phosphorous	Lactate dehydrogenase	
A.	↓	↑	↑	↑	(10%)
B.	↓	↑	↓	↑	(7%)
C.	↑	↓	↓	↑	(2%)
D.	↑	↑	↓	↓	(4%)
E.	↑	↑	↑	↓	(5%)
✓ F.	↑	↑	↑	↑	(69%)

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Acute lymphoblastic leukemia (ALL) is a hematologic malignancy that is generally associated with a high tumor cell burden and a rapid turnover rate. Therefore, initiation of cytotoxic chemotherapy often leads to massive lysis of tumor cells, which spills intracellular contents into the blood (**tumor lysis syndrome**), resulting in the following:

- **Hyperphosphatemia:** Intracellular phosphate concentration is much higher than serum phosphate levels. Therefore, serum phosphate levels typically spike following chemotherapy initiation. Because excess phosphate is excreted via the kidneys, patients are at risk for calcium-phosphate deposition in the renal tubules and collecting system, which can lead to hypocalcemia and acute renal failure.
- **Hyperuricemia:** Purine nucleic acids released from lysed tumor cells are metabolized by xanthine oxidase into uric acid. Because uric acid is excreted through the kidneys and is poorly soluble, patients are at risk for obstructing uric acid stones, which can lead to acute renal injury.
- **Hyperkalemia:** Potassium is primarily an intracellular ion. Therefore, significant tumor lysis is generally associated with elevations of serum potassium, which can lead to cardiac arrhythmia.
- **Elevated lactate dehydrogenase** (LDH): Lactate dehydrogenase, an enzyme involved in cellular respiration, is found in almost all human cells. It is an important laboratory marker for cell lysis in a wide range of disease states (eg, hemolytic anemia). Levels are typically significantly elevated in

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patients are at risk for obstructing uric acid stones, which can lead to acute renal injury.

- **Hyperkalemia:** Potassium is primarily an intracellular ion. Therefore, significant tumor lysis is generally associated with elevations of serum potassium, which can lead to cardiac arrhythmia.
- **Elevated lactate dehydrogenase** (LDH): Lactate dehydrogenase, an enzyme involved in cellular respiration, is found in almost all human cells. It is an important laboratory marker for cell lysis in a wide range of disease states (eg, hemolytic anemia). Levels are typically significantly elevated in tumor lysis syndrome.

Educational objective:

Patients with hematologic malignancies that have high tumor cell burdens or rapid turnover rates are at high risk for electrolyte abnormalities following the initiation of cytotoxic chemotherapy due to the massive lysis of tumor cells. Patients generally develop hyperphosphatemia, hyperkalemia, hyperuricemia, and elevated lactate dehydrogenase.

Physiology	Hematology & Oncology	Tumor lysis syndrome
Subject	System	Topic

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A 23-year-old woman with a history of sickle cell disease comes to the office for follow-up. The patient is homozygous for hemoglobin S and has had frequent episodes of painful vasoocclusive crises. She has no other medical conditions and takes folic acid supplementation. The patient does not use tobacco, alcohol, or illicit drugs. Physical examination shows no abnormalities. Additional therapy with hydroxyurea is planned. This medication is likely to improve this patient's symptoms primarily through which of the following mechanisms?

A. Decreased red blood cell dehydration (1%)
B. Direct inhibition of red blood cell polymerization (5%)
C. Increased hemoglobin A2 synthesis (1%)
✓ D. Increased fetal hemoglobin synthesis (88%)
E. Increased red blood cell antioxidant levels (1%)
F. Stimulation of red blood cell production (0%)

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Main adult hemoglobin



Hemoglobin variants



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Patients with **sickle cell disease** (SCD) have a missense mutation in the beta globin gene that leads to the substitution of valine for glutamic acid in the 6th position of the beta globulin chain. This altered form of hemoglobin is called **hemoglobin S** (Hb S); unlike normal adult hemoglobin (Hb A), Hb S polymerizes when deoxygenated or dehydrated, leading to erythrocyte membrane damage (ie, intravascular **hemolysis**) and clogging of small vessels (ie, painful **vasoocclusive crises**, ischemia).

Heterozygotes for Hb S are usually asymptomatic because there is enough Hb A to prevent extensive polymerization of Hb S, but homozygotes typically have severe disease. These individuals often require repeated blood transfusions for symptomatic anemia and treatment with **hydroxyurea**, an antimetabolite that inhibits the ribonucleotide reductase enzyme. Although inhibition of ribonucleotide reductase leads to the myelosuppressive effects of hydroxyurea (it causes cell cycle arrest in rapidly dividing hematopoietic cells), hydroxyurea also shifts globin gene transcription from the beta globin locus to the **gamma globin** locus (via unclear mechanisms), thereby **increasing** circulating levels of **fetal hemoglobin** (HB F).

HB F is unaffected by the sickle cell mutation (because it is not composed of beta chains) and has physiologic properties similar to hemoglobin A; therefore, hydroxyurea is often used in the treatment of SCD to improve oxygen delivery, reduce vasoocclusive crises, and lessen need for transfusions.

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(Choice A) The calcium-dependent (Gardos) potassium channel regulates the transport of potassium and water through the erythrocyte membrane; blocking this channel could help prevent erythrocyte dehydration but has not been shown to improve symptoms.

(Choice B) Voxelotor directly inhibits polymerization of Hb S by binding to the alpha chain of the molecule and causing an allosteric change that results in increased oxygen binding.

(Choice C) Hb A2 is a variant of normal adult hemoglobin that has 2 delta chains instead of 2 beta chains. Because it does not contain the abnormal beta chains, increased hemoglobin A2 could reduce sickle cell crises. However, hydroxyurea increases gamma globulin expression, not delta globulin expression.

(Choice E) L-glutamine, a precursor to the antioxidant glutathione, reduces oxidative stress in erythrocytes with HB S. It is used for patients with SCD who have persistent vasoocclusive pain or those who cannot tolerate hydroxyurea.

(Choice F) Stimulation of erythrocyte production (eg, erythropoietin) would likely worsen vasoocclusive crises by increasing circulating levels of Hb S. Hydroxyurea inhibits (not stimulates) the production of erythrocytes, leukocytes, and platelets by blocking ribonucleotide reductase; however, patients with SCD still benefit from administration due to stimulated HB F production.

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Educational objective:
Hydroxyurea is used in patients with sickle cell disease to increase expression of gamma globin chains, which leads to increased circulating fetal hemoglobin (Hb F) concentration. This reduces vasoocclusive crises and symptomatic anemia episodes.

Pharmacology	Hematology & Oncology	Sickle cell
Subject	System	Topic

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In vitro studies demonstrate that tumor cell lines can become resistant after exposure to various anticancer agents. These cells express a specific cell surface glycoprotein that has which of the following functions?

A. Tyrosine kinase-coupled receptor (29%)
B. Adenylate cyclase-coupled receptor (8%)
C. Cell adhesion molecule (17%)
D. Transmembrane ion channel (10%)
E. ATP-dependent transporter (32%)

Correct

32%
Answered correctly

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Explanation

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Human tumor cells have developed the ability to resist chemotherapy in much the same way that many bacteria have developed resistance to antibiotics. One well-studied mechanism by which human tumor cells resist these agents is via the human multidrug resistance (MDR1) gene. The prototype product of this gene is P-glycoprotein, a transmembrane protein that functions as an ATP-dependent efflux pump. P-glycoprotein is normally expressed in intestinal and renal tubular epithelial cells and functions to eliminate foreign compounds from the body. This protein is also present in the capillary endothelium of the vessels that form the blood-brain barrier. In this location, P-glycoprotein prevents the penetration of foreign compounds into the CNS. In tumor cells, this ATP-powered transmembrane pump protein actively removes chemotherapeutic agents, particularly hydrophobic agents like the anthracyclines.

Drugs such as verapamil, diltiazem, and ketoconazole, among others, have been shown to reduce the action of this multidrug resistance protein in experimental models; the development of agents specifically intended to abolish this mechanism of resistance is currently underway.

(Choice A) Tyrosine kinase receptors generally mediate the effects of hormones that promote anabolism and cell growth such as insulin, insulin-like growth factor 1, epidermal growth factor, platelet-derived growth factor, and others.

(Choice B) cAMP is the second messenger in the G-protein / adenylate cyclase second messenger

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(Choice B) cAMP is the second messenger in the G-protein / adenylate cyclase second messenger system. This system is utilized by numerous hormone receptors including beta-adrenergic receptors, V2 ADH receptors, and calcitonin, glucagon, TSH, ACTH, and HCG receptors, among many others.

(Choice C) Cell adhesion molecules (CAMs) are proteins located on the cell surface that mediate binding with other cells or with the extracellular matrix. Examples include selectins, integrins, and cadherins. Cell adhesion molecules are generally downregulated in malignant tumors, which allows these cells to spread from their site of origin.

(Choice D) Transmembrane ion channels selectively allow certain ions to pass into or out of the cell. These channels facilitate the formation of a voltage gradient across the cell membrane. Examples of ion channels, transporters, and exchangers are ubiquitous. These proteins participate in the formation of urine, nerve and myocyte depolarization, muscle contraction, sweat formation, exocrine secretion formation, and many other processes.

Educational Objective:
The human multidrug resistance (MDR1) gene codes for P-glycoprotein, a transmembrane ATP-dependent efflux pump protein that has a broad specificity for hydrophobic compounds. This protein can both reduce the influx of drugs into the cytosol and can increase efflux from the cytosol, thereby preventing the action of

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Pharmacology	Hematology & Oncology	Chemotherapy
Subject	System	Topic

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A 20-year-old man is evaluated for recurrent episodes of jaundice. He was separated from his parents at a young age and is unaware of any family medical history. The patient resided in several foster homes throughout his childhood but currently lives alone. His temperature is 36.7 C (98 F), blood pressure is 120/80 mm Hg, and pulse is 72/min. Physical examination shows pallor, icterus, and mild splenomegaly. There is no lymphadenopathy or hepatomegaly. The remainder of the physical examination is normal. Laboratory test results are as follows:

Hemoglobin	9 g/L
Platelets	198,000/mm^3
Leukocytes	6500/mm^3
Lactate dehydrogenase	Increased
Total bilirubin	3.4 mg/dL
Direct bilirubin	0.2 mg/dL
Aspartate aminotransferase (AST)	25 U/L

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Direct bilirubin	0.2 mg/dL
Aspartate aminotransferase (AST)	25 U/L
Alanine aminotransferase (ALT)	30 U/L
Direct Coombs test	Negative

When the patient's red blood cells are incubated in a hypotonic solution with glycerol, hemoglobin is released. The control sample does not release hemoglobin. This patient is at greatest risk of developing which of the following?

A. Autoimmune disease (3%)
B. Autoinfarction of the spleen (18%)
C. Avascular necrosis of the femur (2%)
D. Hemolysis from consumption of fava beans (20%)
E. Pigmented gallstones (56%)

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Hereditary spherocytosis	
Epidemiology	• Autosomal dominant inheritance (~75%) • Northern European descent
Clinical presentation	• Hemolytic anemia • Jaundice • Splenomegaly
Laboratory findings	• ↑ **Mean corpuscular hemoglobin concentration** • **Spherocytes** on peripheral smear • Negative Coombs test • ↑ Osmotic fragility on **acidified glycerol lysis test**
Treatment	• Splenectomy
Complications	• Pigmented gallstones • Aplastic crises from parvovirus B19 infection

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This patient's presentation with anemia, elevated lactate dehydrogenase, and indirect hyperbilirubinemia suggests hemolytic anemia. The lysing of blood cells when incubated in hypotonic saline with glycerol

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This patient's presentation with anemia, elevated lactate dehydrogenase, and indirect hyperbilirubinemia suggests hemolytic anemia. The lysing of blood cells when incubated in hypotonic saline with glycerol describes a positive acidified glycerol lysis test, the diagnostic test for **hereditary spherocytosis (HS)**. Spherocytes demonstrate **increased osmotic fragility** in this test due to their decreased surface area to volume ratio.

HS is the most common hemolytic anemia due to a **red blood cell (RBC) membrane defect**. The mutation in HS most often affects **spectrin** and **ankyrin**, the plasma-membrane scaffolding proteins. Patients with HS present with **hemolytic anemia, jaundice**, and **splenomegaly**. **Pigmented gallstones** are a complication of any hemolytic anemia. In chronic hemolysis, the increased bilirubin from lysed RBCs precipitates as calcium bilirubinate, forming pigmented stones in the gallbladder. Patients with HS may also present with aplastic crises due to parvovirus B19 infection.

(Choice A) Autoimmune hemolytic anemia (AIHA) results in findings similar to those seen in HS (eg, indirect hyperbilirubinemia, elevated lactate dehydrogenase, spherocytes on peripheral blood smear). In contrast to HS, AIHA is not heritable, and patients have a positive direct antiglobulin (Coombs) test along with a propensity to develop autoimmune disease (eg, systemic lupus erythematosus).

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(Choices B and C) The abnormal adhesion of sickle cell RBCs to the endothelium and the subsequent obstruction of small blood vessels lead to various injuries, which include splenic autoinfarction and femoral avascular necrosis. A positive acidified glycerol lysis test classically describes HS, not sickle cell anemia.

(Choice D) Glucose-6-phosphate dehydrogenase (G6PD) deficiency presents with hemolytic anemia and indirect hyperbilirubinemia usually following oxidative stress. Common triggers include drugs (sulfonamide or antimalarial agents), fava beans, and infections (viral hepatitis, pneumonia, or typhoid). Peripheral smears of G6PD deficiency anemia show bite cells and Heinz bodies, not spherocytes.

Educational objective:
Hereditary spherocytosis results from red cell cytoskeleton abnormalities, most commonly in the proteins spectrin and ankyrin. Increased osmotic fragility on acidified glycerol lysis testing confirms the diagnosis. Hemolytic anemia, jaundice, and splenomegaly are classic manifestations. Complications include pigmented gallstones and aplastic crises from parvovirus B19 infection.

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References

- Hereditary spherocytosis

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A 42-year-old man is hospitalized with fever and persistent sore throat. On physical examination, his temperature is 38.3 C (101 F), blood pressure is 120/80 mm Hg, pulse is 94/min, and respirations are 16/min. There are several bruises on his trunk, and blood is oozing from his intravenous catheter venipuncture sites. His blood fibrinogen level is 110 mg/dL (normal 150-400 mg/dL). Bone marrow biopsy shows a predominance of immature myeloid cells with azurophilic needle-shaped cytoplasmic granules. Chromosomal analysis of these immature cells is most likely to show which of the following abnormalities?

A. t(8;14) (3%)
B. t(9;22) (14%)
C. t(14;18) (6%)
D. t(15;17) (75%)
E. inv(16) (0%)

Correct

75%
Answered correctly

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Explanation

This patient, who has fever (suggesting infection and possibly low leukocyte count) and bruising/oozing from venipuncture sites (suggesting low platelet count) associated with low fibrinogen levels and immature myeloid cells, likely has disseminated intravascular coagulation (DIC) in the setting of **acute promyelocytic leukemia (APL)**. APL, a subtype of acute myelogenous leukemia (AML), is characterized by the presence in the bone marrow of promyelocytes (**immature** myeloid cells) that typically contain needle-shaped cytoplasmic inclusions known as **Auer rods** (fused lysosomal granules). A classic presentation is bleeding in the setting of **DIC**, a consumptive coagulopathy characterized by **decreased fibrinogen levels**, increased fibrin degradation products, prolonged prothrombin time and partial thromboplastin time, and thrombocytopenia that is generally not low enough to result in spontaneous bleeding by itself.

APL is most commonly associated with a t(15;17) chromosomal translocation that causes fusion of the retinoic acid receptor-α (RARA) gene to the promyelocyte leukemia (PML) gene. APL is referred to as AML **M3** in the French-American-British (FAB) classification of leukemia and is responsive to all-trans retinoic acid therapy.

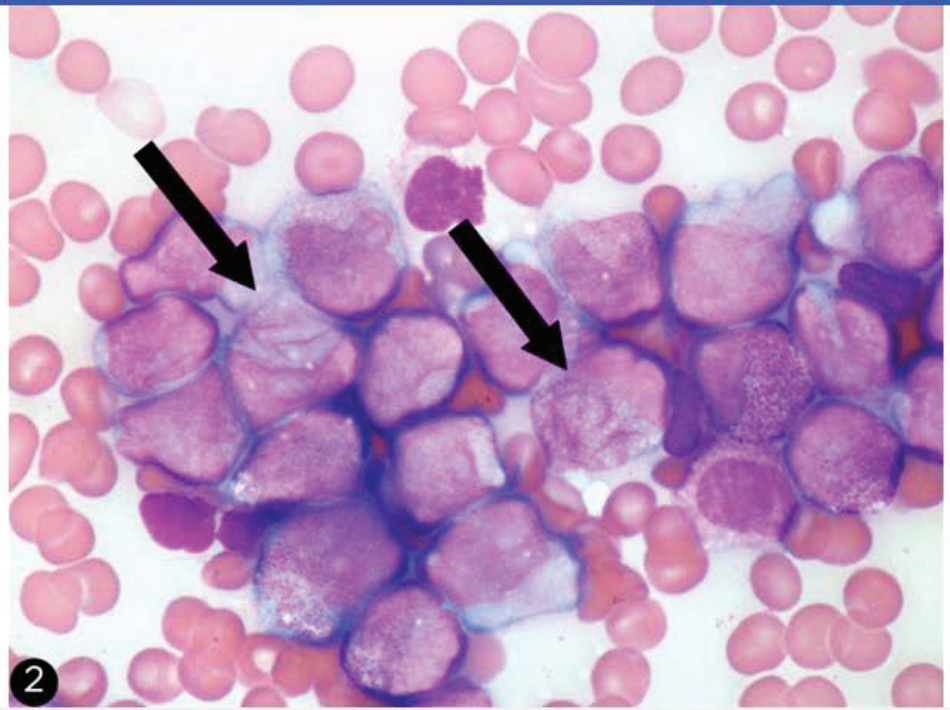
(Choice A) t(8;14) occurs in ~80% of cases of Burkitt lymphoma and results in movement of the *myc*

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M3 in the French-American-British (FAB) classification of leukemia and is responsive to all-trans retinoic acid therapy.

(Choice A) t(8;14) occurs in ~80% of cases of Burkitt lymphoma and results in movement of the *myc* protooncogene from chromosome 8 to a region near the immunoglobulin promoter site on chromosome 14.

(Choice B) t(9;22) forms the Philadelphia chromosome associated with chronic myelogenous leukemia (CML). The BCR-ABL fusion protein results from this cytogenetic defect. Auer rods are not typically present in CML, in which mature myeloid forms are generally seen. Most patients with CML present in the chronic, stable phase (eg, nonspecific symptoms, abdominal fullness, leukocytosis).

(Choice C) t(14;18) is associated with non-Hodgkin follicular small cleaved cell lymphoma. This abnormality places the BCL-2 protooncogene from chromosome 18 near the immunoglobulin heavy chain promoter region on chromosome 14.

(Choice E) A chromosome 16 inversion is observed in the M4Eo (eosinophilic) subtype of AML.

Educational objective:
Acute promyelocytic leukemia (APL, M3 acute myeloid leukemia) can present with persistent infection and coagulopathy causing hemorrhagic signs and symptoms. Bone marrow biopsy classically reveals promyelocytes with intracytoplasmic Auer rods. APL is associated with a t(15;17) chromosomal

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Educational objective:
Acute promyelocytic leukemia (APL, M3 acute myeloid leukemia) can present with persistent infection and coagulopathy causing hemorrhagic signs and symptoms. Bone marrow biopsy classically reveals promyelocytes with intracytoplasmic Auer rods. APL is associated with a t(15;17) chromosomal translocation that causes fusion of the retinoic acid receptor-α gene and promyelocyte leukemia gene.

Pathology	Hematology & Oncology	Acute promyelocytic leukemia
Subject	System	Topic

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A 13-month-old boy is brought to the clinic after repeated infections for the past 4 months, including otitis media, pneumonia, and erysipelas. Although his infections have been responsive to treatment, his father is concerned about the number of infections. The patient also has persistent diarrhea, and a recent stool antigen detection assay was positive for *Giardia lamblia*. An immunoglobulin panel demonstrates very low serum levels of all immunoglobulin types. Intradermal injection of *Candida* antigens results in a large indurated nodule within 48 hours. This patient's lymph nodes most likely lack which of the following structures?

A. Germinal centers (79%)
B. Outer cortex (5%)
C. Paracortical zone (13%)
D. Subcapsular sinuses (0%)
E. Trabeculae (0%)

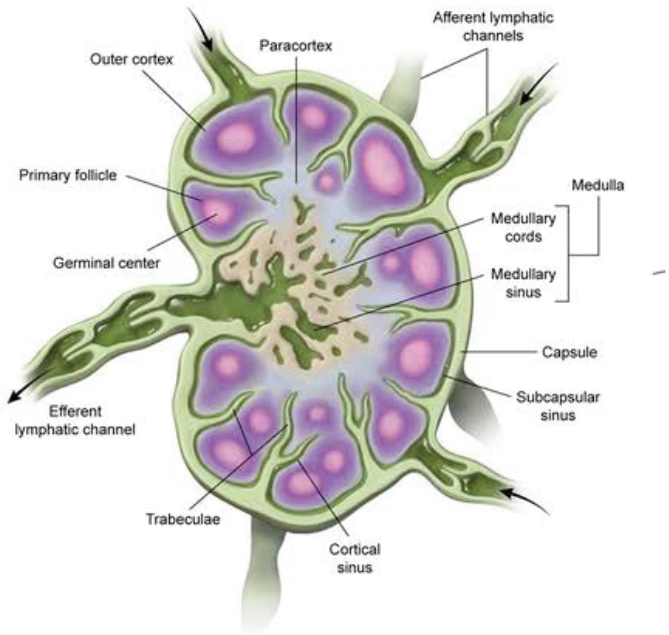
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Exhibit Display

Lymph node anatomy



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This patient's **recurrent infections** in the setting of intact T lymphocyte function (positive response to *Candida* antigens) and very low immunoglobulin levels suggest **X-linked (Bruton) agammaglobulinemia** (XLA). This condition results from a mutation in the Bruton tyrosine kinase gene that causes failure of bone marrow pre-B cells to develop into mature B lymphocytes. As a result, patients have absent or very low B lymphocytes in the peripheral blood and lymphoid tissues.

In general, B lymphocytes aggregate in the cortex of lymph nodes to form lymphoid follicles. Primary follicles are dense and dormant; secondary follicles have a pale germinal center containing proliferating B cells in response to an antigenic stimulus. In XLA, primary lymphoid follicles and **germinal centers do not form** due to an **absence of B cells**.

Lack of mature B lymphocytes also leads to inability to produce plasma cells, and patients therefore have absent or **very low serum immunoglobulins**. Recurrent infections typically begin once maternally derived antibodies wane (age 3-6 months), as seen here.

(Choice B) The outer cortex is composed of primary and secondary lymphoid follicles (ie, B cell–rich regions), but it also contains prominent numbers of CD4+ T cells within the interfollicular regions (allowing for T-B cell interaction). In patients with XLA, the outer cortex is present but diminished.

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regions), but it also contains prominent numbers of CD4+ T cells within the interfollicular regions (allowing for T-B cell interaction). In patients with XLA, the outer cortex is present but diminished.

(Choice C) The paracortical zone lies internal to the cortex of the lymph node. This zone is populated primarily by T lymphocytes and dendritic cells. Dendritic cells present antigens collected from the blood and lymph to the T lymphocytes aggregated in this section of the node. This patient's positive reaction to *Candida* antigens (type 4 hypersensitivity) indicates intact T lymphocyte function.

(Choices D and E) The subcapsular sinuses are found between the capsule and the cortex of the lymph node and are in direct communication with afferent lymphatic vessels. These sinuses are connected to cortical sinuses that line the trabeculae and penetrate through the cortex and paracortex to reach the medulla. From there, medullary sinuses drain into the efferent lymphatic channel. These structures are not affected in XLA.

Educational objective:

X-linked (Bruton) agammaglobulinemia is caused by a defect in B cell maturation, resulting in absent mature B cells and severely low immunoglobulin levels. T cell numbers and function remain intact. Due to the absence of B cells, primary lymphoid follicles and germinal centers do not form within lymph nodes.

References

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A 9-year-old boy with beta thalassemia major comes to the office for a routine red blood cell transfusion. He was diagnosed at age 6 months and has since received numerous blood transfusions and chelation therapies. The patient has tolerated each transfusion and chelation therapy well with no immediate reactions or side effects. Vital signs are normal. On physical examination, the boy has mild frontal bossing, hepatosplenomegaly, and jaundice. A recent liver biopsy showed Kupffer cells containing coarse, yellowish-brown cytoplasmic granules. The granules are most likely composed of which of the following?

A. Amyloid (0%)
B. Bilirubin (7%)
C. Copper (2%)
D. Glycogen (0%)
E. Glycolipid (0%)
F. Hemosiderin (80%)
G. Lipofuscin (7%)

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Patients with **chronic hemolytic anemia** (eg, beta thalassemia major) depend on recurrent **red blood cell (RBC) transfusions** to maintain an adequate hemoglobin level. **Iron overload (hemosiderosis)** from increased iron absorption is a common complication resulting from both the primary condition (eg, hemolysis) and its treatment (frequent RBC transfusions).

Circulating iron is carried by transferrin. Once deposited in cells, iron binds to apoferritin to form ferritin micelles. Because iron is utilized poorly in patients with thalassemia and cannot be excreted actively, the ferritin micelles accumulate in macrophages of the reticuloendothelial system. The resulting iron-storage complex is known as **hemosiderin** and microscopically appears as **brown or yellowish-brown pigments** in either granular or crystalline form. Hemosiderin can be identified histologically with a Prussian-blue stain. In the liver, hemosiderin is typically seen in **Kupffer cells** (hepatic macrophages that line the walls of the sinusoids and participate in RBC breakdown).

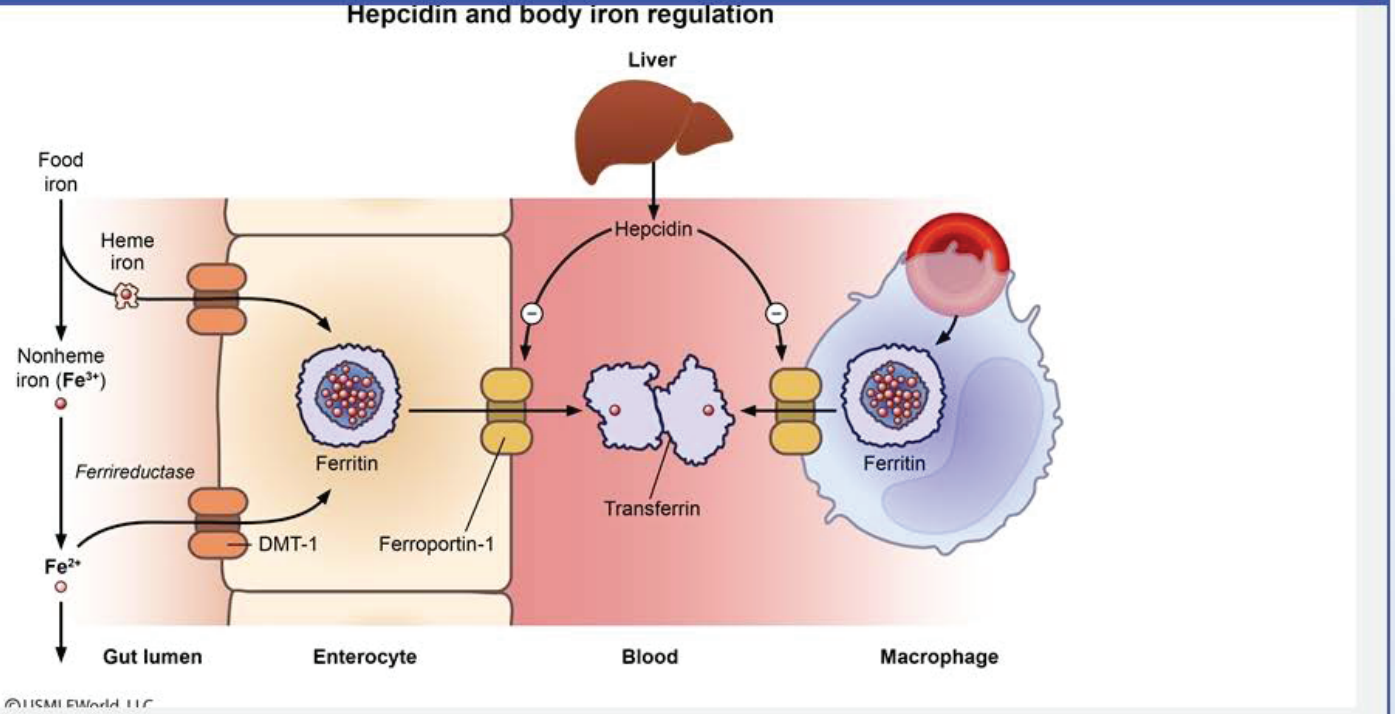
Patients receiving regular transfusions should undergo routine iron **chelation therapy** to reduce the overall iron load within the body and improve survival. Eventually, the iron burden will overwhelm the reticuloendothelial cells' capacity to sequester iron, resulting in parenchymal iron overload in the liver, myocardium, skin, and pancreas (eg, "bronze diabetes").

(Choice A) Amyloid protein has a pale rose color after Congo red staining. Accumulation of amyloid fibrils

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[Choice A] Amyloid protein has a pale rose color after Congo red staining. Accumulation of amyloid fibrils

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(Choice A) Amyloid protein has a pale rose color after Congo red staining. Accumulation of amyloid fibrils can result in a variety of sequelae (eg, cardiomyopathy, nephrotic syndrome).

(Choice B) Bilirubin is the primary pigment found within bile and is a byproduct of hemoglobin breakdown. Hemolytic anemia commonly results in indirect hyperbilirubinemia and jaundice.

(Choice C) Copper accumulation is seen in Wilson disease, an autosomal recessive disease characterized by cirrhosis and neurologic complications.

(Choice D) Glycogen appears as clear cytoplasmic vacuoles and stains pinkish purple with the periodic acid-Schiff reaction. Glycogen is abundant in the liver shortly after a meal.

(Choice E) Patients with Gaucher disease (glucocerebrosidase enzyme deficiency) have pancytopenia, hepatosplenomegaly, and pathologic fractures. The cardinal histologic finding are Gaucher cells (black arrows), which are macrophages laden with cerebrosides and other glycolipids.

(Choice G) Lipofuscin is an insoluble yellow-brown pigment composed of lipids and phospholipids complexed with proteins. This pigment accumulates with age and "wear and tear" of multiple organs.

Educational objective:
Iron overload (hemosiderosis) is a common and serious complication of chronic hemolytic anemia and

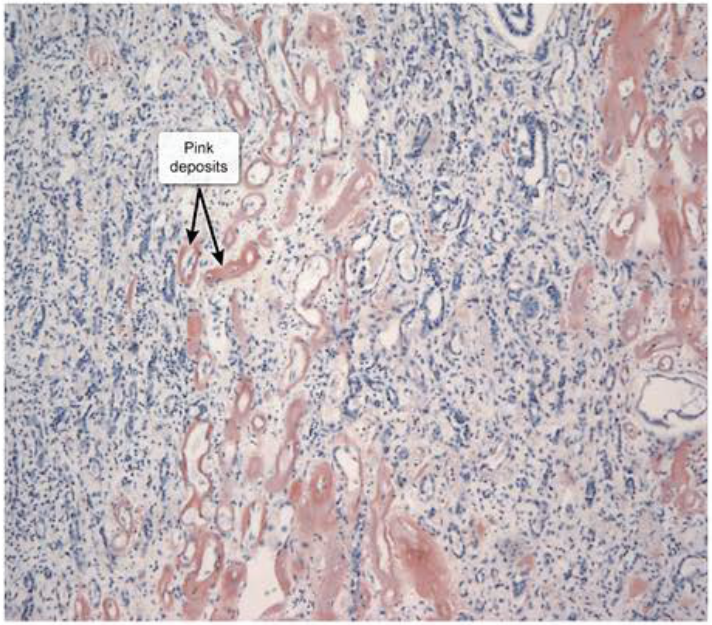
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Exhibit Display

Amyloid



Congo red stain without polarization ©UWorld

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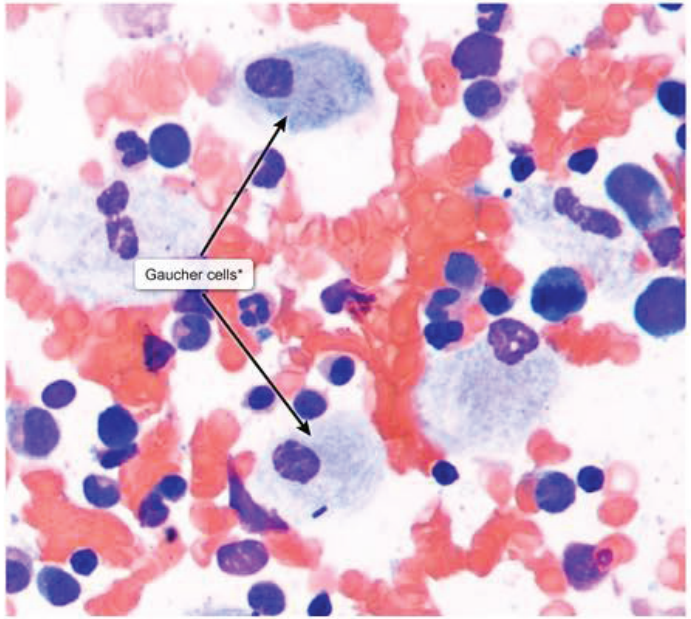
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Exhibit Display

Gaucher disease



*"Wrinkled tissue paper" cytoplasm due to glucocerebroside accumulation within lysosomes ©UWorld

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Exhibit Display

Lipofuscin



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(Choice C) Copper accumulation is seen in Wilson disease, an autosomal recessive disease characterized by cirrhosis and neurologic complications.

(Choice D) Glycogen appears as clear cytoplasmic vacuoles and stains pinkish purple with the periodic acid-Schiff reaction. Glycogen is abundant in the liver shortly after a meal.

(Choice E) Patients with Gaucher disease (glucocerebrosidase enzyme deficiency) have pancytopenia, hepatosplenomegaly, and pathologic fractures. The cardinal histologic finding are Gaucher cells (black arrows), which are macrophages laden with cerebrosides and other glycolipids.

(Choice G) Lipofuscin is an insoluble yellow-brown pigment composed of lipids and phospholipids complexed with proteins. This pigment accumulates with age and "wear and tear" of multiple organs.

Educational objective:

Iron overload (hemosiderosis) is a common and serious complication of chronic hemolytic anemia and frequent blood transfusions. Hemosiderin accumulation is the cardinal histologic finding. Chelation therapy is indicated to reduce parenchymal iron deposition.

References

- Iron overload syndromes and the liver.

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A 66-year-old man with hypertension and stage IV chronic kidney disease comes to the office for follow-up. The patient has had worsened fatigue and low energy over the past several months but no chest pain or shortness of breath. He was previously nonadherent with antihypertensive therapy but has been following treatment recommendations since renal dysfunction was diagnosed 2 years ago. Blood pressure is 126/78 mm Hg and pulse is 68/min. Cardiac auscultation reveals an S4 sound. The rest of the physical examination is unremarkable. Laboratory results show normocytic, normochromic anemia with a low reticulocyte count. Serum iron studies are within normal limits. Treatment with a recombinant glycoprotein hormone is begun, and repeat laboratory testing several weeks later shows an improvement in hemoglobin level. The effects of the hormone prescribed for this patient are most likely mediated by which of the following pathways?

A. Adenylate cyclase/cyclic AMP (6%)

B. Arachidonic acid/phospholipase A2 (1%)

C. Janus kinase 2/signal transducers and activators of transcription (73%)

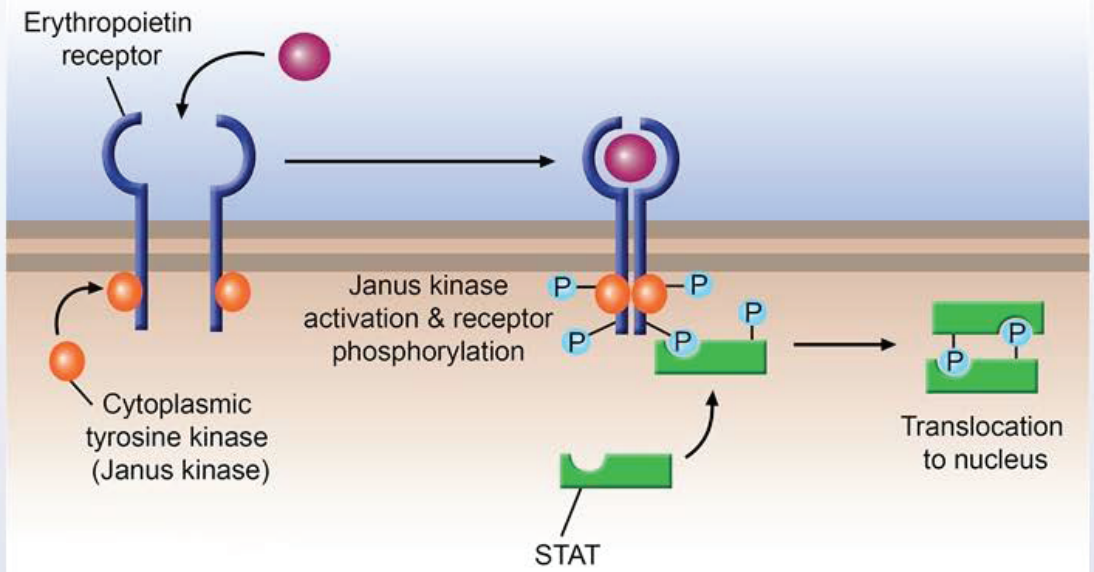
D. Nuclear receptors (10%)

E. Phosphatidylinositol 3-kinase (2%)

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Erythropoietin signal transduction



STAT = signal transducers and activators of transcription.

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Patients with **chronic kidney disease** (CKD) often develop **normocytic anemia** as the glomerular filtration rate declines, due to an inability to generate adequate quantities of erythropoietin (EPO). EPO is a glycoprotein produced by peritubular fibroblast cells in the renal cortex in response to tissue hypoxia (as seen with anemia). Healthy individuals increase EPO production up to 10,000-fold in response to anemia, but patients with CKD have chronic renal inflammation that **damages EPO-producing cells**, thereby preventing an adequate EPO response. Therefore, patients with CKD are often treated with **recombinant EPO agents** (eg, epoetin, darbepoetin) to supplement EPO production.

EPO travels from the kidney through the bloodstream to the bone marrow, where it binds to a surface receptor on **erythrocyte colony–forming unit cells** (erythrocyte precursors). Binding activates the Janus kinase 2/signal transducers and activators of transcription (**JAK2/STAT**) signaling pathway, which induces the transcription of proteins that inhibit erythrocyte precursor apoptosis and promote survival. Binding also activates signals that increase the differentiation of erythrocyte precursors into mature erythrocytes. Together, these effects increase the production of erythrocytes and improve circulating red blood cell counts.

Activating mutations affecting the *JAK2* gene are associated with polycythemia vera, a chronic myeloproliferative disorder marked by the clonal proliferation of erythrocytes (leading to dramatic elevations

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Activating mutations affecting the *JAK2* gene are associated with polycythemia vera, a chronic myeloproliferative disorder marked by the clonal proliferation of erythrocytes (leading to dramatic elevations in hematocrit).

(Choice A) Cyclic AMP mediates the effects of a variety of hormones including glucagon, antidiuretic hormone (V2 receptor), and corticotropin. However, this pathway is not a primary intermediate in erythrogenesis.

(Choice B) Cleavage of membrane phospholipids by phospholipase A2 leads to the formation of arachidonic acid, which is in turn converted into prostaglandins and leukotrienes that help regulate the inflammatory response. A variety of medications directly or indirectly affect this system, including glucocorticoids, nonsteroidal anti-inflammatory drugs, and leukotriene inhibitors.

(Choice D) Widely used therapeutic hormones that activate a nuclear receptor include thyroid hormone, vitamins A & D, and the steroid hormones (eg, glucocorticoids, mineralocorticoids, sex hormones).

(Choice E) Therapeutic hormones that activate a phosphatidylinositol second messenger system include antidiuretic hormone (V1 receptor), gonadotropin-releasing hormone, and oxytocin.

(Choice F) The Ras/mitogen-activated protein kinase signal transduction system is used by a variety of

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vitamins A & D, and the steroid hormones (eg, glucocorticoids, mineralocorticoids, sex hormones).

(Choice E) Therapeutic hormones that activate a phosphatidylinositol second messenger system include antidiuretic hormone (V1 receptor), gonadotropin-releasing hormone, and oxytocin.

(Choice F) The Ras/mitogen-activated protein kinase signal transduction system is used by a variety of growth factors (eg, epidermal growth factor, platelet-derived growth factor), which primarily act to stimulate cell proliferation. Uncontrolled activation of this system can lead to malignancy.

Educational objective:
Chronic kidney disease is commonly associated with normocytic anemia due to reduced production of erythropoietin by the kidneys. Erythropoietin signal transduction is primarily mediated by the Janus kinase 2/signal transducers and activators of transcription (JAK2/STAT) pathway, which promotes erythrocyte precursor survival.

References

- Urology and nephrology update: anemia of chronic kidney disease.

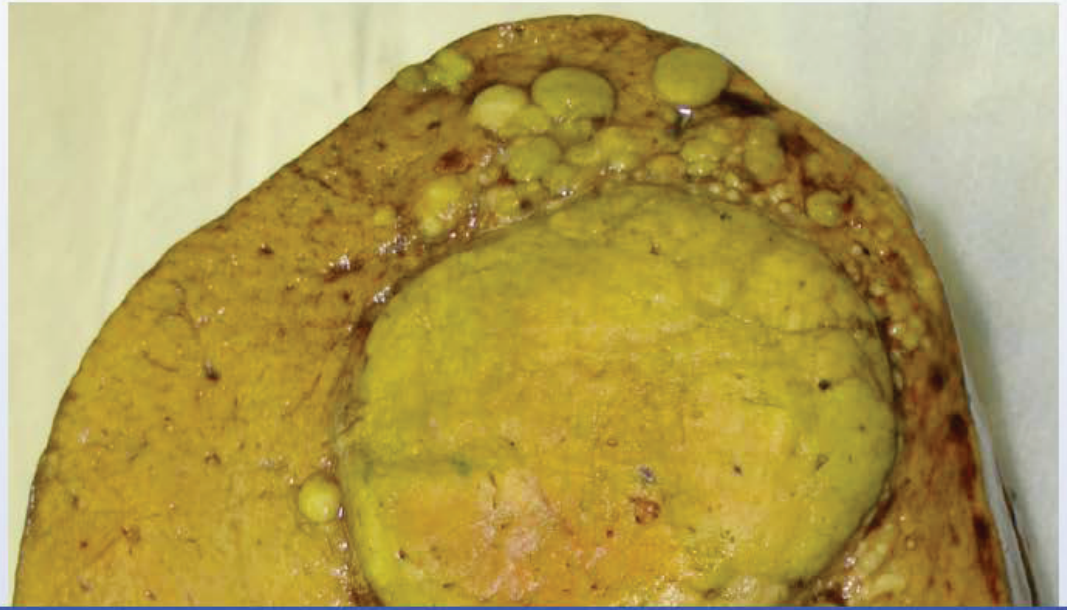
Physiology	Hematology & Oncology	Chronic kidney disease
Subject	System	Topic

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A 64-year-old man is brought to the hospital by ambulance after being found unresponsive by his brother. Despite resuscitative efforts, he dies shortly thereafter. The family reports that the patient had 2 months of progressive fatigue and an unintentional weight loss prior to the episode. Autopsy examination reveals a massive pulmonary embolus, and a cross-section of the liver shows the following:



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Genomic analysis of the hepatic lesions demonstrates intranuclear fragments of foreign DNA. These fragments most likely belong to which of the following pathogens?

A. Cytomegalovirus (4%)

B. ~~*Entamoeba histolytica*~~ (15%)

C. Epstein-Barr virus (6%)

D. Hepatitis B virus (50%)

E. ~~Hepatitis C virus~~ (22%)

F. ~~Human papilloma virus~~ (0%)

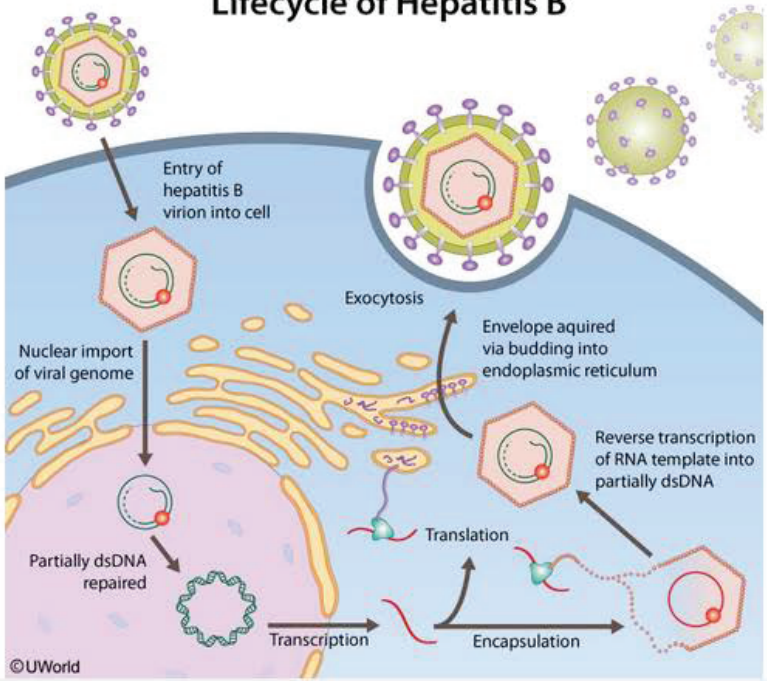
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Exhibit Display

Lifecycle of Hepatitis B



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The cross-section of the liver shows a large, solid, yellow-green nodule with multiple smaller nodules, consistent with **hepatocellular carcinoma** (HCC). Chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infections dramatically increase the risk of HCC. Ongoing infection with either virus leads to **increased hepatocyte turnover** and the generation of local inflammatory cytokines, which can result in genetic mutations that lead to malignant transformation. However, **HBV** has several additional mechanisms that promote HCC, including the following:

- **Integration into the host genome** – Nearly 90% of patients with chronic HBV who develop HCC have evidence of HBV DNA in the chromosomes of tumor cells. HBV is a partially double-stranded DNA virus that is repaired by into a closed circular DNA strand. HBV DNA is often inserted into the cellular genome, although this is not required for viral replication (unlike HIV). Integration into regions that control cell growth and differentiation can result in tumorigenesis.
- **Production of oncogenic viral proteins** – HBV produces a viral protein called **HBx** that is a transcriptional activator of several genes associated with cellular growth. It also interferes with the function of p53, an important tumor-suppressor protein.

(Choices A and C) Cytomegalovirus and Epstein-Barr virus are members of the *Herpesviridae* family. Both have double-stranded DNA genomes and cause acute infection followed by latent infection.

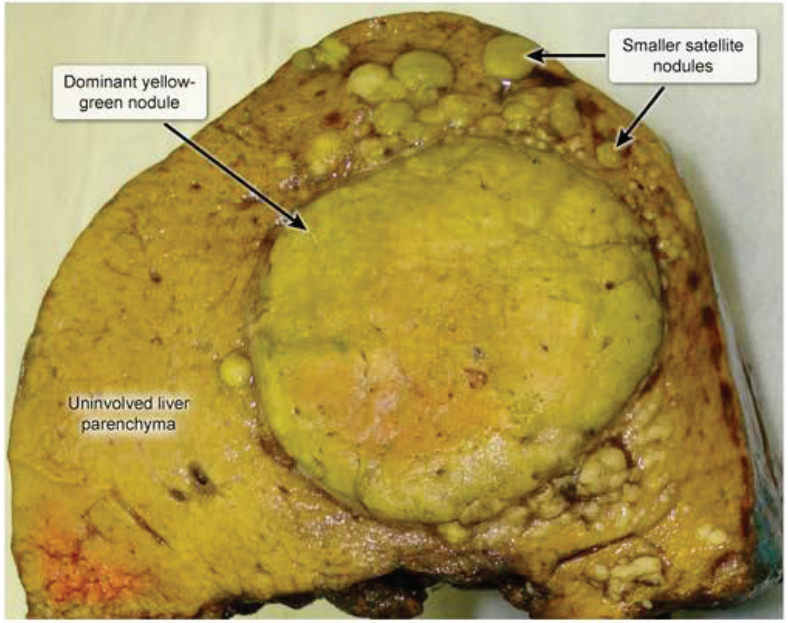
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Hepatocellular carcinoma



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function of p53, an important tumor-suppressor protein.

(Choices A and C) Cytomegalovirus and Epstein-Barr virus are members of the *Herpesviridae* family. Both have double-stranded DNA genomes and cause acute infection followed by latent infection. Cytomegalovirus is not particularly associated with cancer, but Epstein-Barr infection is linked to nasopharyngeal carcinoma and hematologic malignancies. However, neither virus is strongly associated with development of HCC.

(Choice B) *Entamoeba histolytica* is a protozoal infection that is typically acquired by ingesting contaminated food or water in developing countries. A minority of patients develops invasive disease with liver abscess. This usually presents with fever and right-upper quadrant pain. The organism does not incorporate its genome into host cells.

(Choice E) Chronic HCV infection dramatically increases the risk of HCC. However, HCV is an RNA virus (that does not have reverse transcriptase) and is unable to integrate into the host genome.

(Choice F) Human papilloma virus is a double-stranded DNA virus of the papillomavirus family. HPV produces oncogenic proteins and is able to integrate into the host chromosome. However, HPV is not linked with liver cancer; it typically causes cervical and oropharyngeal cancer.

Educational objective:

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liver abscess. This usually presents with fever and right-upper quadrant pain. The organism does not incorporate its genome into host cells.

(Choice E) Chronic HCV infection dramatically increases the risk of HCC. However, HCV is an RNA virus (that does not have reverse transcriptase) and is unable to integrate into the host genome.

(Choice F) Human papilloma virus is a double-stranded DNA virus of the papillomavirus family. HPV produces oncogenic proteins and is able to integrate into the host chromosome. However, HPV is not linked with liver cancer; it typically causes cervical and oropharyngeal cancer.

Educational objective:

Both hepatitis B (HBV) and hepatitis C virus infections increase the risk of hepatocellular carcinoma due to chronic hepatic inflammation and cell turnover. HBV is also carcinogenic due to the production of oncogenic proteins and the insertion of the HBV genome into host chromosomes.

References

- Role of hepatitis B virus DNA integration in human hepatocarcinogenesis.

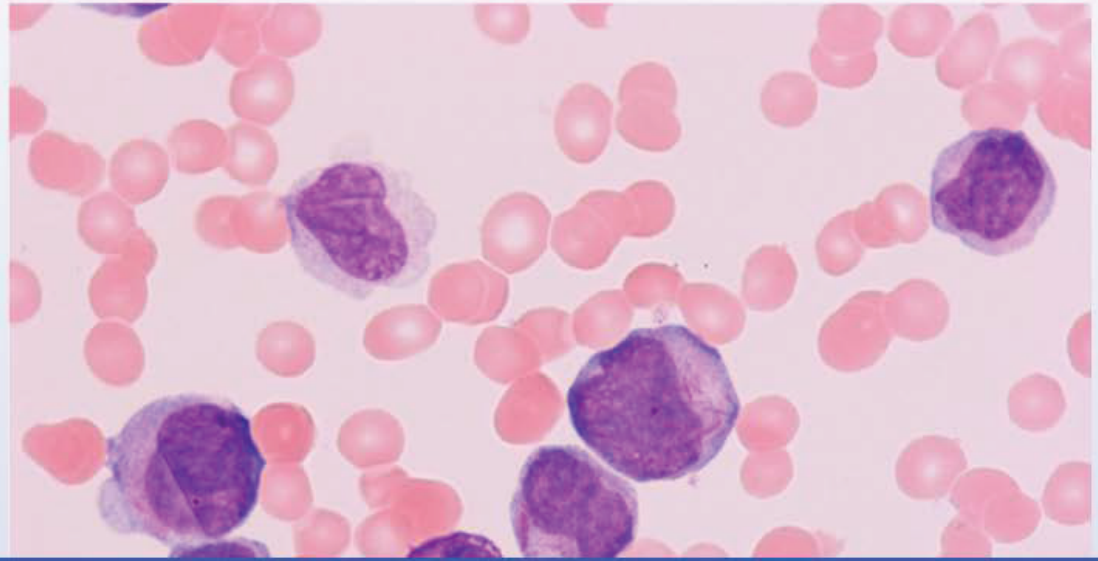
Pathology	Hematology & Oncology	Hepatocellular cancer
Subject	System	Topic

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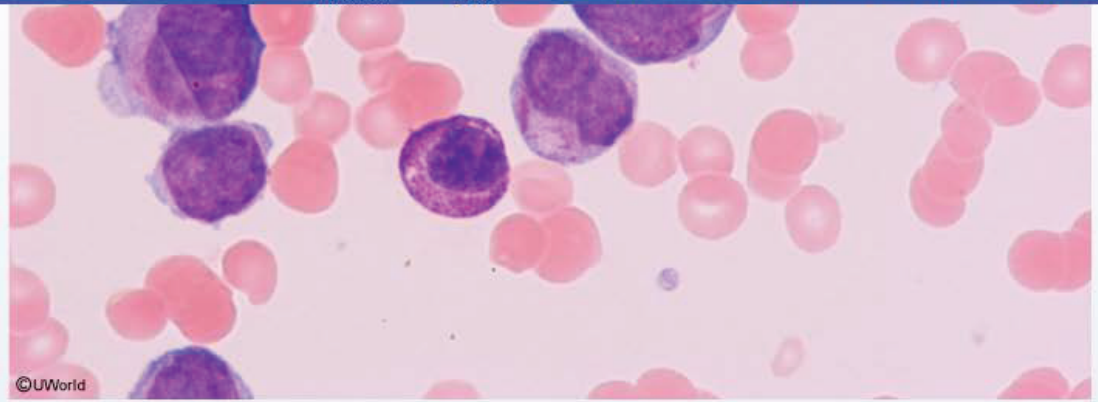
A 43-year-old man comes to the hospital due to recurrent episodes of fever and sore throat despite multiple courses of antibiotic therapy. For the past several months, he has also felt "run down" and fatigued all the time. His wife adds that he bruises easily and has had bleeding gums on several occasions. His temperature is 37.8 C (100.2 F). On examination, he has mucosal pallor, pharyngeal erythema, and multiple ecchymoses on his extremities. His peripheral blood smear is shown in the image below.



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Which of the following chromosomal abnormalities is most likely present in the affected cells?

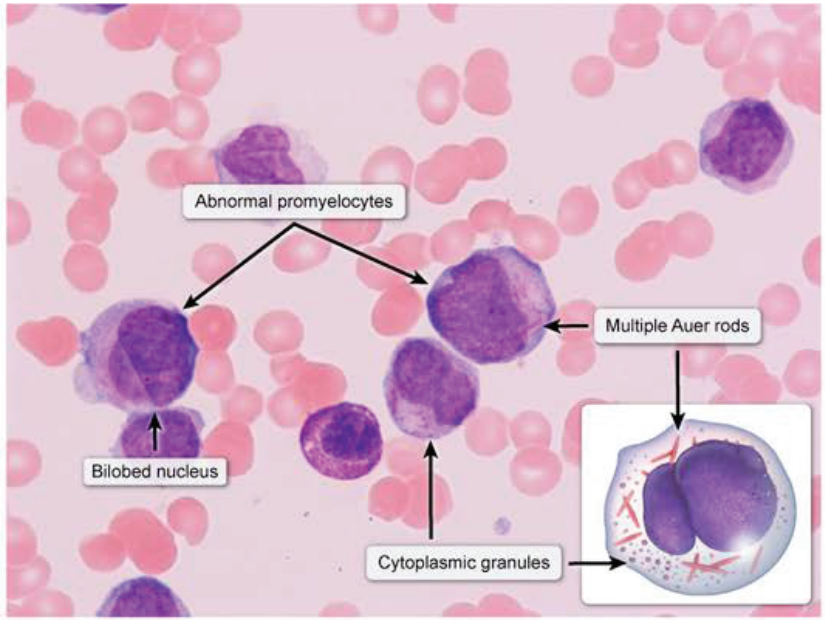
- A. t(8;14) (6%)
- B. t(9;22) (21%)
- C. t(11;14) (5%)
- ✓ D. t(15;17) (66%)
- E. 13q- (0%)

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Acute promyelocytic leukemia



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This patient has recurrent infections (possibly reflecting neutropenia), pallor (anemia), and ecchymoses (thrombocytopenia), with a peripheral blood smear that shows several abnormal myelocyte precursors containing coarse rod-shaped intracytoplasmic granules called **Auer rods**. This presentation is characteristic of **acute myelogenous leukemia** (AML). The **M3** variant of AML, **acute promyelocytic leukemia** (APML), characterized by the presence of promyelocytes on smear, is associated with disseminated intravascular coagulation (bleeding, thrombocytopenia, prolonged prothrombin and activated thromboplastin time). Affected cells exhibit the cytogenetic abnormality **t(15;17)**.

This cytogenetic change represents a translocation between the retinoic acid receptor alpha (*RARα*) gene on chromosome 17 and the promyelocytic leukemia (*PML*) gene on chromosome 15. Fusion of these 2 genes produces a chimeric gene product, *PML/RARα*, which codes for an abnormal retinoic acid receptor. This abnormal fusion gene inhibits promyelocyte differentiation and triggers the development of APML. Management is with all-trans retinoic acid.

(Choice A) With t(8;14), associated with Burkitt lymphoma, there is a translocation between the c-*Myc* protooncogene on chromosome 8 and the Ig heavy chain region on chromosome 14. This leads to increased production of the oncogene due to the frequency with which the Ig gene is transcribed.

(Choice B) Translocation of the *ABL* gene from chromosome 9 to chromosome 22 is characteristic of

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protooncogene on chromosome 8 and the Ig heavy chain region on chromosome 14. This leads to increased production of the oncogene due to the frequency with which the Ig gene is transcribed.

(Choice B) Translocation of the *ABL* gene from chromosome 9 to chromosome 22 is characteristic of chronic myelogenous leukemia. t(9;22) forms the "Philadelphia chromosome" and results in the formation of a new gene, *BCR-ABL*, whose product has tyrosine kinase activity.

(Choice C) Mantle cell lymphoma is a B-cell malignancy associated with t(11;14). This translocation results in activation of the cyclin D gene.

(Choice E) Deletion of 13q is one of the molecular defects seen in chronic lymphocytic leukemia.

Educational objective:
The presence of rod-shaped intracytoplasmic inclusions known as Auer rods is characteristic of many forms of acute myeloblastic leukemia (AML). The M3 variant of AML, acute promyelocytic leukemia, is associated with the cytogenetic abnormality t(15;17).

Pathology	Hematology & Oncology	Acute promyelocytic leukemia
Subject	System	Topic

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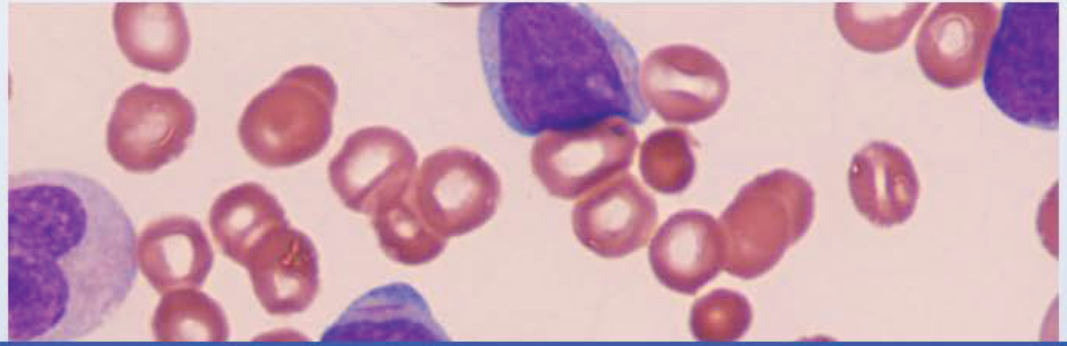
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A 63-year-old man comes to the office due to fatigue and easy bruising. He has no lymphadenopathy on physical examination. Laboratory results are as follows:

Complete blood count

Hemoglobin	8.0 g/dL
Platelets	40,000/mm^3
Leukocytes	20,500/mm^3

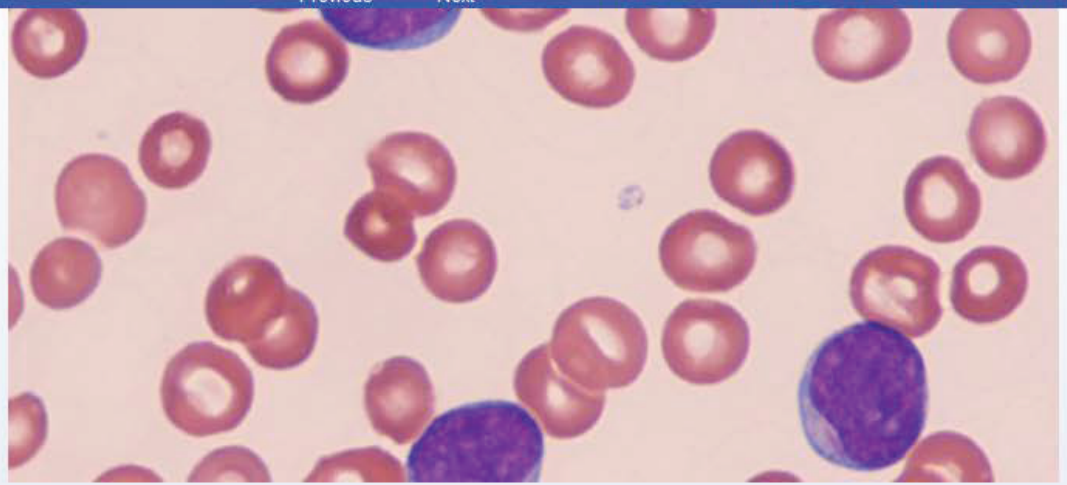
The patient's peripheral blood smear is shown in the image below:



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Which of the following is the most likely diagnosis?

A. Acute lymphoblastic leukemia (6%)

B. Acute myelogenous leukemia (51%)

C. Chronic lymphocytic leukemia (18%)

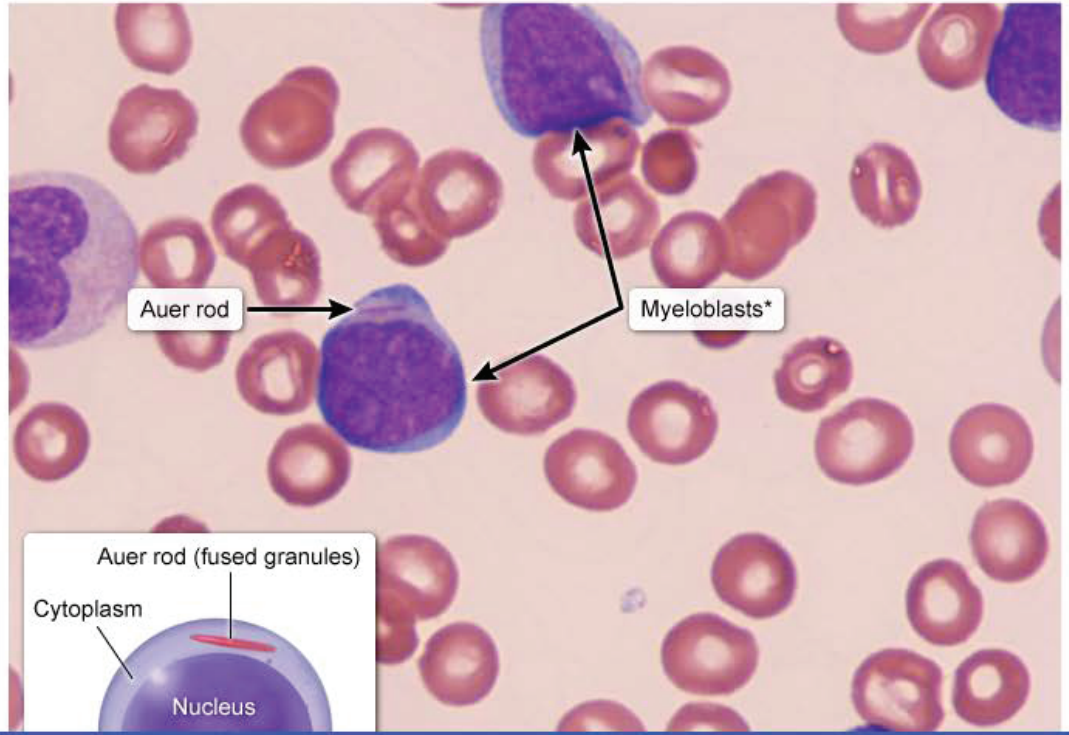
D. Chronic myelogenous leukemia (16%)

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Acute myeloid leukemia



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High nuclear-to-cytoplasmic ratio; fine chromatin; and visible nucleoli

This patient's peripheral blood smear shows very large nucleated cells (see red cell size for comparison) with scant cytoplasm. These are **blast cells**, the finding of which makes acute leukemia likely. Closer examination of the smear reveals linear, purple-red inclusions in some of the cells, called **Auer rods**. These may be single or multiple within immature myeloid precursors. Auer rods are highly suggestive of **acute myelogenous leukemia (AML)** but not of acute lymphoblastic leukemia (ALL) **(Choice A)**. Although Auer rods are most commonly associated with the M1, M2, and M3 subtypes of AML, they may be found in any type of AML.

The vast majority of AML cases occur in adults, with a median age of 65. Most patients present with complications of pancytopenia (eg, fatigue from anemia, bruising/bleeding from thrombocytopenia, infection from possible functional neutropenia despite leukocytosis). The median white blood cell count is around 15,000/mm^3 at diagnosis. Current World Health Organization diagnostic criteria require the presence of ≥20% myeloblasts in the bone marrow.

(Choices C and D) Chronic leukemia causes a prevalence of mature cells in the peripheral blood. In chronic myelogenous leukemia (CML), peripheral smears show many mature granulocytes and few blasts (generally <2%). In chronic lymphocytic leukemia (CLL), smears show many mature lymphocytes.

(Choice E) Patients with hairy cell leukemia have splenomegaly, cytopenias, and circulating hairy cells

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chronic myelogenous leukemia (CML), peripheral smears show many mature granulocytes and few blasts (generally <2%). In chronic lymphocytic leukemia (CLL), smears show many mature lymphocytes.

(Choice E) Patients with hairy cell leukemia have splenomegaly, cytopenias, and circulating hairy cells. On peripheral blood smear, hairy cells take the appearance of small- to medium-sized lymphoid cells with circumferential "hairy" projections.

(Choice F) Patients with Hodgkin lymphoma generally present with a mass (eg, mediastinal mass, enlarged lymph nodes). The finding of circulating neoplastic cells is extremely rare. Histologically, Reed-Sternberg cells are characteristic. These are large cells with an abundant basophilic cytoplasm and ≥2 nuclear lobes or nuclei.

(Choice G) Patients with infectious mononucleosis have fatigue, lymphadenopathy, and splenomegaly. Thrombocytopenia can be a complication of this infection. Peripheral blood smear will show few circulating atypical lymphocytes, but no blasts.

Educational objective:
The finding of Auer rods (linear purple-red inclusions within immature myeloid precursors) is helpful in making the diagnosis of acute myeloid leukemia. Auer rods are not found in acute lymphoblastic leukemia. In chronic myelogenous leukemia, there are more mature cells and fewer blasts.

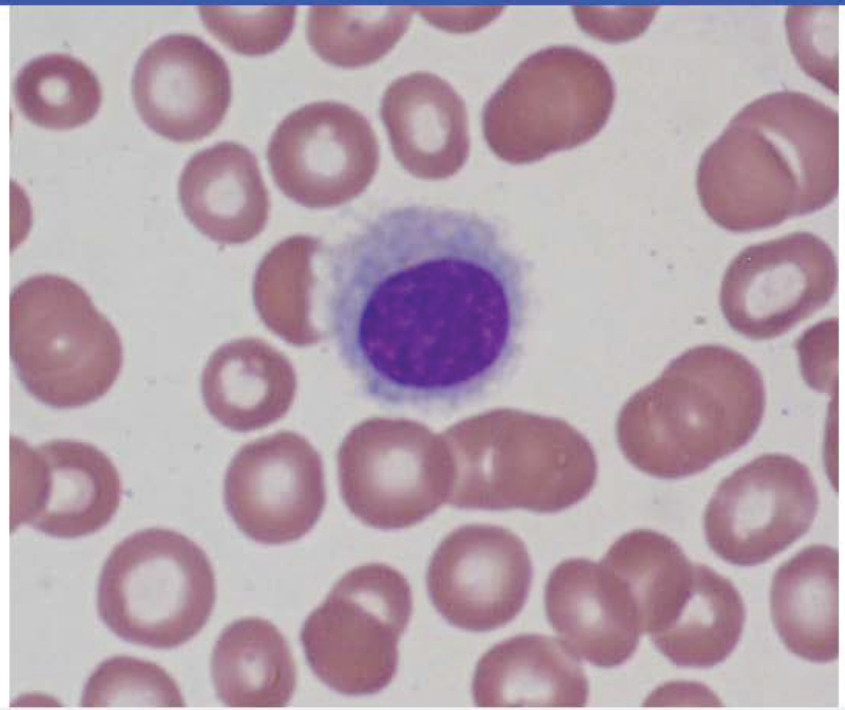
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chronic myelogenous leukemia (CML), peripheral smears show many mature granulocytes and few blasts.

Exhibit Display



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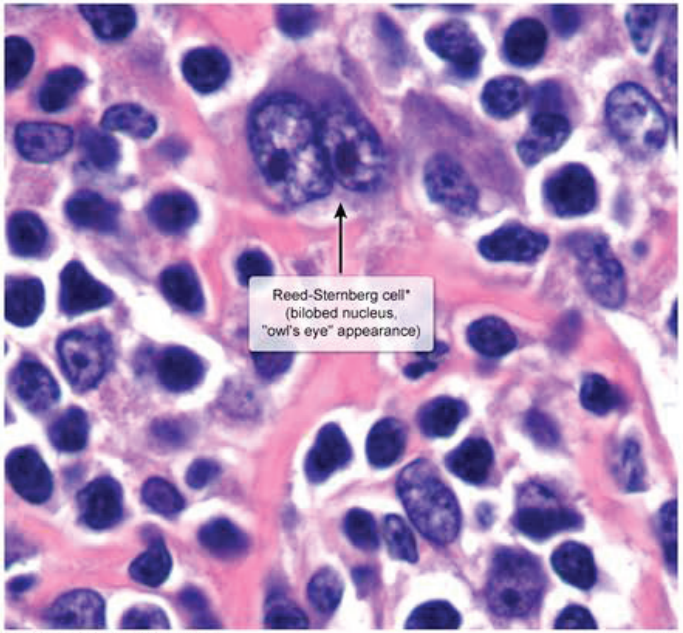
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chronic myelogenous leukemia (CML), peripheral smears show many mature granulocytes and few blasts.

Exhibit Display

Hodgkin lymphoma



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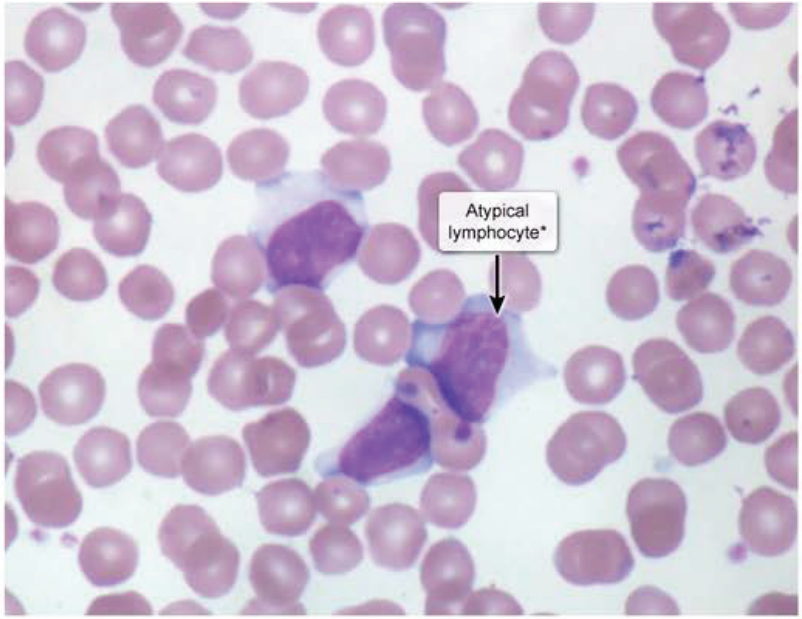
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chronic myelogenous leukemia (CML), peripheral smears show many mature granulocytes and few blasts.

Exhibit Display

Atypical lymphocytes



*Large reactive lymphocyte with abundant blue cytoplasm

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circumferential "hairy" projections.

(Choice F) Patients with Hodgkin lymphoma generally present with a mass (eg, mediastinal mass, enlarged lymph nodes). The finding of circulating neoplastic cells is extremely rare. Histologically, Reed-Sternberg cells are characteristic. These are large cells with an abundant basophilic cytoplasm and ≥2 nuclear lobes or nuclei.

(Choice G) Patients with infectious mononucleosis have fatigue, lymphadenopathy, and splenomegaly. Thrombocytopenia can be a complication of this infection. Peripheral blood smear will show few circulating atypical lymphocytes, but no blasts.

Educational objective:
The finding of Auer rods (linear purple-red inclusions within immature myeloid precursors) is helpful in making the diagnosis of acute myeloid leukemia. Auer rods are not found in acute lymphoblastic leukemia. In chronic myelogenous leukemia, there are more mature cells and fewer blasts.

Pathology	Hematology & Oncology	Acute myeloid leukemia
Subject	System	Topic

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Band forms	10%
Myelocytes	3%
Metamyelocytes	1%
Lymphocytes	15%

The leukocyte alkaline phosphatase test score is elevated. Which of the following is the most likely finding on this patient's peripheral blood smear?

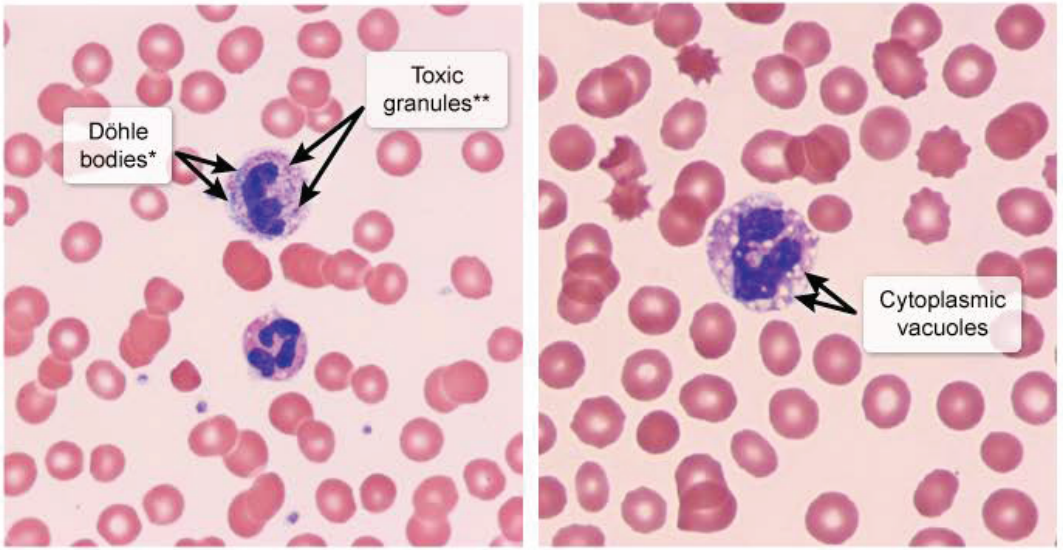
A. Basophilic oval inclusions in mature neutrophils (41%)
B. ~~Basophilic stippling of red blood cells~~ (4%)
C. Mature neutrophils with hypersegmented nuclei (20%)
D. ~~Numerous blasts with azurophilic rods~~ (24%)
E. Small lymphoid cells with cleaved nuclei (9%)

41%
02 mins, 30 secs
09/04/2020

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Reactive neutrophils



*Blue cytoplasmic inclusions of rough endoplasmic reticulum
**Large, dark purple granules

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This patient most likely has pneumonia with sepsis and an associated **leukemoid reaction**, a significant leukocytosis (may exceed 50,000/mm^3) that occurs in response to an underlying inflammatory condition

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**Large, dark purple granules

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This patient most likely has pneumonia with sepsis and an associated **leukemoid reaction**, a significant leukocytosis (may exceed 50,000/mm^3) that occurs in response to an underlying inflammatory condition (eg, severe **infection**, hemorrhage, solid tumors). Release of colony-stimulating factors and inflammatory mediators into the circulation causes the bone marrow to increase the production of leukocytes, resulting in **leukocytosis**.

Blood smear typically shows numerous **mature neutrophils**, which may have reactive morphologic features, such as **Döhle bodies** (blue cytoplasmic inclusions of rough endoplasmic reticulum), toxic granulation, and cytoplasmic vacuoles. Increased neutrophil precursors (eg, bands, metamyelocytes, myelocytes) are also typically present (referred to as "**left shift**") due to early release from the marrow in response to the increased demand of the inflammatory condition.

Assessment of **leukocyte alkaline phosphatase** (an enzyme found in maturing neutrophils) can be used to distinguish marked leukocytosis due to leukemoid reaction from chronic myeloid leukemia (CML). Values are typically **normal or increased** in leukemoid reaction; in contrast, they are usually low in CML because the abnormal maturing neutrophils have decreased levels of this enzyme.

(Choice B) Basophilic stippling refers to small, blue granules (ribosomal precipitates) in the cytoplasm of

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(Choice B) Basophilic stippling refers to small, blue granules (ribosomal precipitates) in the cytoplasm of red blood cells. It is most often seen in thalassemia, alcohol use disorder, and lead/heavy metal poisoning. This patient's acute presentation and laboratory results are more consistent with leukemoid reaction.

(Choice C) Hypersegmented neutrophils show ≥6 nuclear lobes and are a feature of megaloblastic anemia, often due to vitamin B_{12} or folate deficiency. This patient's normal hemoglobin makes this unlikely.

(Choice D) The presence of numerous blasts with cytoplasmic Auer rods (fused azurophilic granules) in the blood smear would be concerning for acute myeloid leukemia. This patient's laboratory results show mainly mature neutrophils with increased neutrophil precursors (eg, bands, metamyelocytes, myelocytes) but not blasts.

(Choice E) Small lymphoid cells with cleaved nuclei are seen in certain types of lymphoma, particularly follicular lymphoma, a mature B-cell neoplasm. This patient's clinical symptoms and neutrophilia with left shift are more consistent with leukemoid reaction.

Educational objective:
Leukemoid reaction is a significant leukocytosis (may exceed 50,000/mm^3) that occurs in response to an underlying condition, commonly severe infection. Blood smear often shows neutrophilia with reactive

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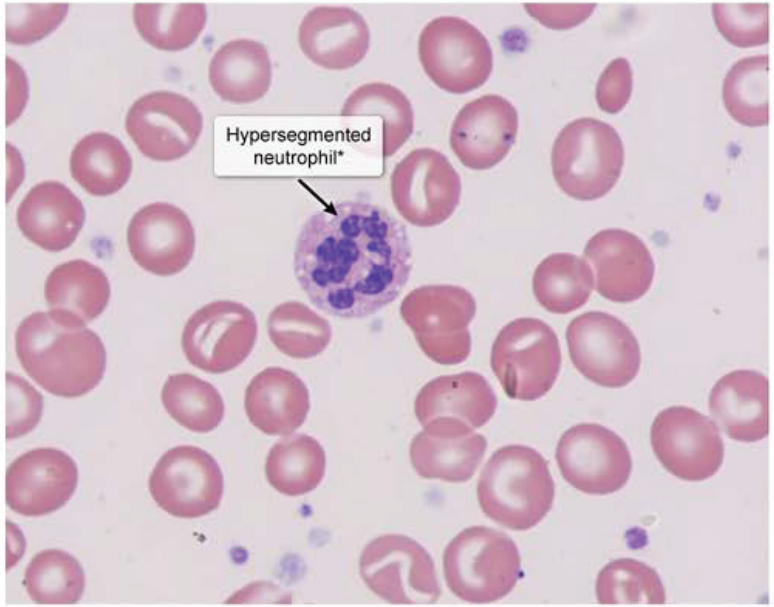
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(Choice B) Basophilic stippling refers to small, blue granules (ribosomal precipitates) in the cytoplasm of

Exhibit Display

Megaloblastic anemia



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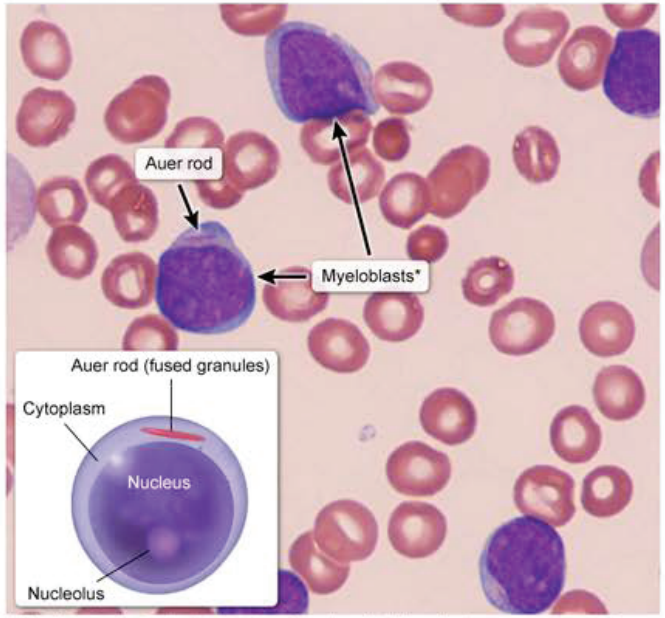
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poisoning. This patient's acute presentation and laboratory results are more consistent with leukemoid

Exhibit Display

Acute myeloid leukemia



*High nuclear-to-cytoplasmic ratio, immature chromatin, and visible nucleoli

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(Choice C) Hypersegmented neutrophils show ≥6 nuclear lobes and are a feature of megaloblastic anemia, often due to vitamin B_{12} or folate deficiency. This patient's normal hemoglobin makes this unlikely.

(Choice D) The presence of numerous blasts with cytoplasmic Auer rods (fused azurophilic granules) in the blood smear would be concerning for acute myeloid leukemia. This patient's laboratory results show mainly mature neutrophils with increased neutrophil precursors (eg, bands, metamyelocytes, myelocytes) but not blasts.

(Choice E) Small lymphoid cells with cleaved nuclei are seen in certain types of lymphoma, particularly follicular lymphoma, a mature B-cell neoplasm. This patient's clinical symptoms and neutrophilia with left shift are more consistent with leukemoid reaction.

Educational objective:

Leukemoid reaction is a significant leukocytosis (may exceed 50,000/mm^3) that occurs in response to an underlying condition, commonly severe infection. Blood smear often shows neutrophilia with reactive features (eg, Döhle bodies), as well as increased neutrophil precursors (eg, bands, metamyelocytes, myelocytes). The leukocyte alkaline phosphatase score is normal or increased.

References

- An update on the etiology and diagnostic evaluation of a leukemoid reaction.

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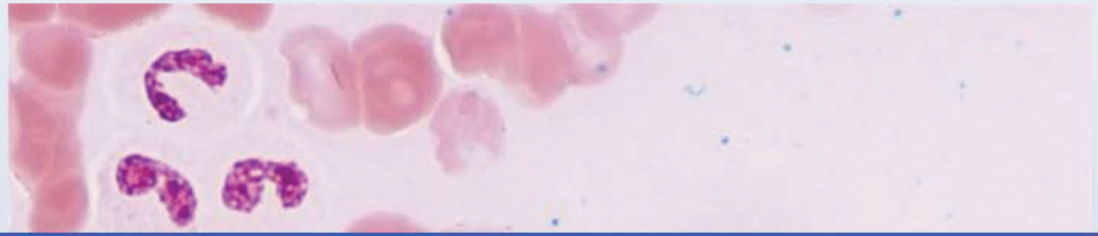
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A 40-year-old woman comes to the office with a 3-month history of progressively limited physical activity due to fatigue. The patient says, "I could barely walk from my car to the office." Medical history is significant for a positive tuberculin skin test 7 months ago with a normal chest radiograph. She has been compliant with the prescribed treatment despite its bitter taste. Physical examination shows a tired-appearing woman with conjunctival and palmar pallor. Complete blood count is as follows:

Hemoglobin	9 g/dL
Hematocrit	28%
Mean corpuscular volume	72 fL

A bone marrow aspirate representative of this patient's disease process is shown below (Prussian blue stain).

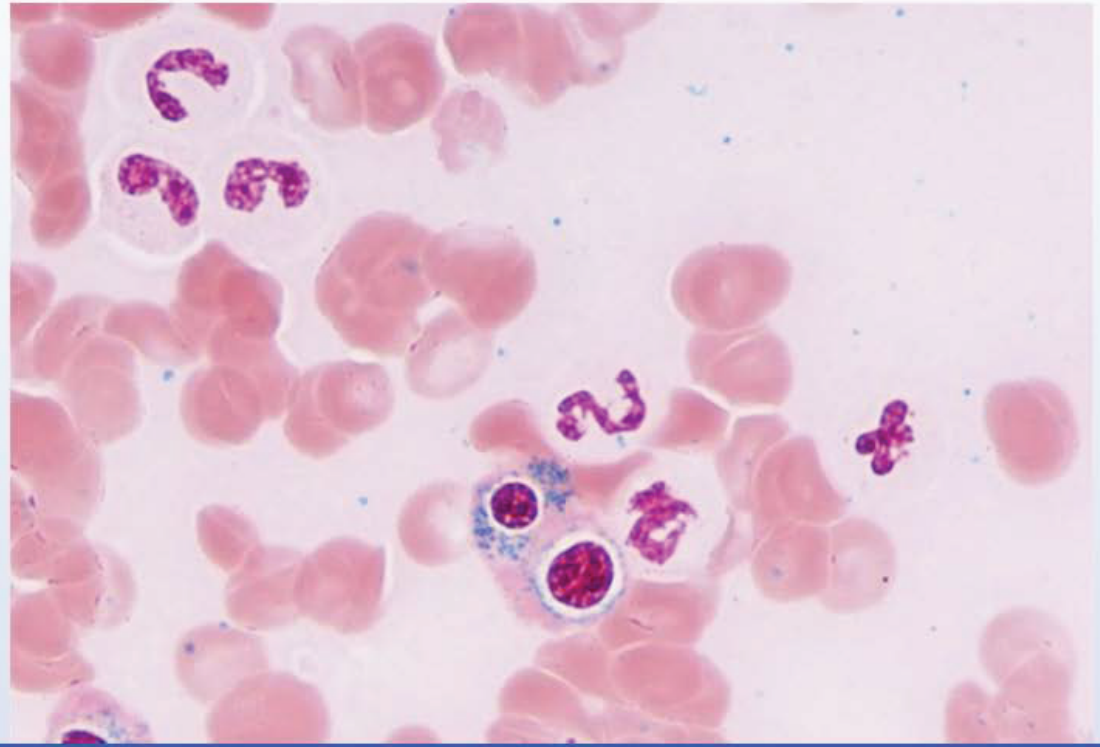


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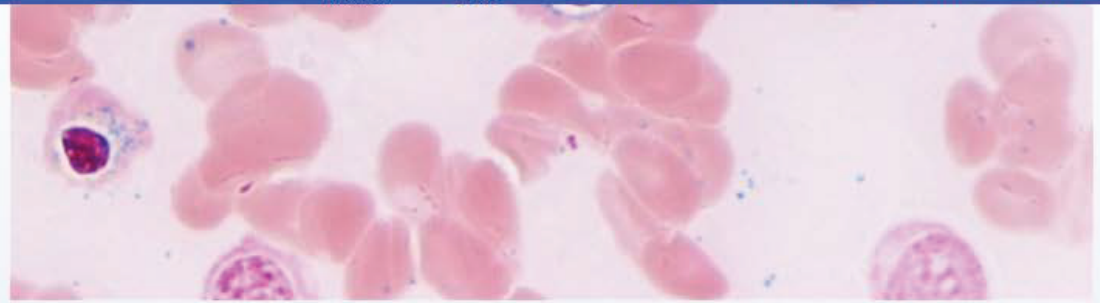
A bone marrow aspirate representative of this patient's disease process is shown below (Prussian blue stain).



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Decreased activity of which of the following enzymes most likely explains the anemia found in this patient?

A. δ-aminolevulinic acid dehydratase (19%)

B. δ-aminolevulinic acid synthase (60%)

C. Cystathionine synthase (5%)

D. Glucose-6-phosphate dehydrogenase (11%)

E. Pyruvate kinase (2%)

Correct

60%

01 min, 27 secs

09/08/2020

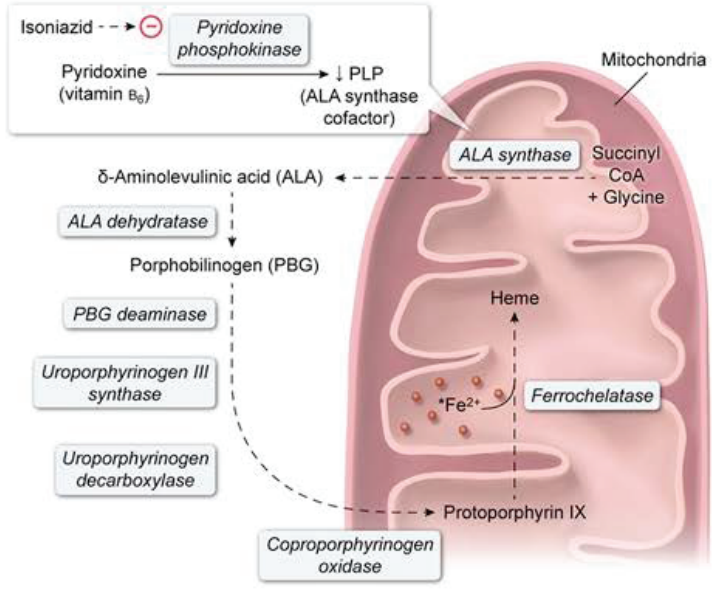
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Exhibit Display

Isoniazid-induced sideroblastic anemia



*Accumulation of excess iron results in ring sideroblasts
PLP = pyridoxal 5' phosphate (active form of vitamin B_6)

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*Accumulation of excess iron results in ring sideroblasts
PLP = pyridoxal 5' phosphate (active form of vitamin B_6)
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This patient with **latent tuberculosis** has laboratory values and bone marrow aspirate findings consistent with **sideroblastic anemia** due to isoniazid use.

Sideroblastic anemia is caused by **impaired heme production** within red blood cells. When iron is transported to developing erythrocytes that cannot form heme, **iron granules** accumulate in mitochondria circumferentially around the nucleus, forming **ring sideroblasts** that can be seen on Prussian blue–stained bone marrow aspirate. Etiologies include X-linked sideroblastic anemia (due to an δ-aminolevulinic acid synthase mutation), myelodysplastic syndrome, alcohol use disorder, copper deficiency, and certain medications (eg, isoniazid, chloramphenicol, linezolid).

Isoniazid directly inhibits the enzyme pyridoxine phosphokinase, which normally converts **pyridoxine** (vitamin B_6) to its active form, pyridoxal 5' phosphate. Pyridoxine is a cofactor for **δ-aminolevulinic acid (ALA) synthase**, the enzyme that catalyzes the rate-limiting step in heme synthesis. Inhibition of this enzyme impairs heme production and erythroid development to produce a **microcytic anemia**. Pyridoxine deficiency can also lead to seborrheic dermatitis, glossitis, and peripheral neuropathy. Therefore, pyridoxine is typically prescribed with isoniazid.

(Choice A) δ-aminolevulinic acid dehydratase is another enzyme involved in heme synthesis. Lead

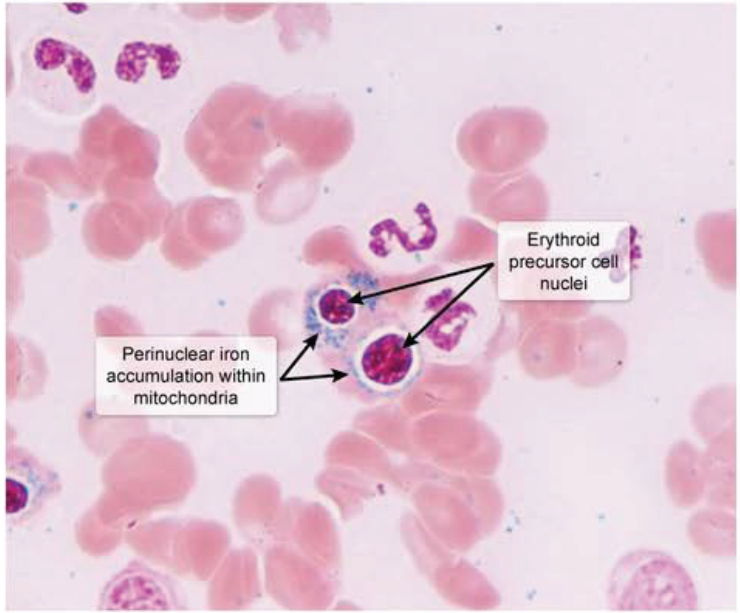
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*Accumulation of excess iron results in ring sideroblasts

Exhibit Display

Ring sideroblasts



Bone marrow aspirate – Prussian blue stain

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(Choice A) δ-aminolevulinic acid dehydratase is another enzyme involved in heme synthesis. Lead

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(Choice A) δ-aminolevulinic acid dehydratase is another enzyme involved in heme synthesis. Lead poisoning can cause anemia by directly inhibiting this enzyme. However, pyridoxine is not a cofactor for this step; therefore, isoniazid would not affect its activity.

(Choice C) Cystathionine synthase catalyzes the formation of cystathionine from homocysteine. Deficiency results in homocystinuria, an autosomal recessive disorder characterized by a marfanoid body habitus and hypercoagulability. Although cystathionine synthase is a pyridoxine-dependent enzyme, impairment does not result in sideroblastic anemia.

(Choice D) Glucose-6-phosphate dehydrogenase (G6PD) deficiency results in increased red blood cell susceptibility to oxidative stress (eg, infection, medication, fava beans), which triggers hemolysis. This results in a normocytic, normochromic, hemolytic anemia without ring sideroblasts.

(Choice E) Pyruvate kinase deficiency, an autosomal recessive disorder, results in a normocytic, normochromic, hemolytic anemia without ring sideroblasts.

Educational objective:

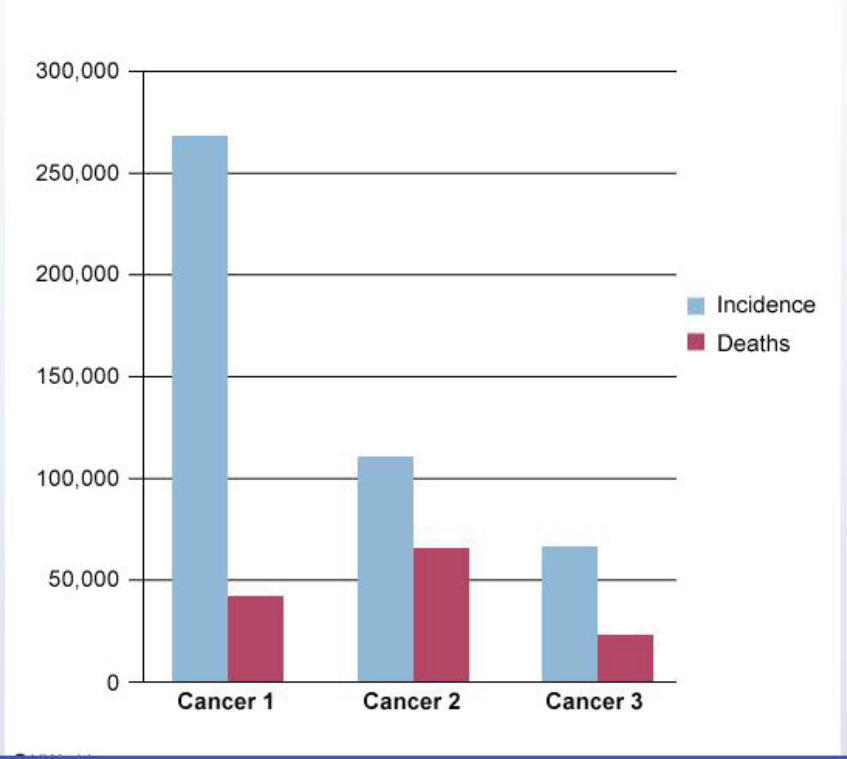
Isoniazid inhibits pyridoxine phosphokinase, leading to impaired activation of pyridoxine (vitamin B_6). Pyridoxine is a cofactor for δ-aminolevulinic acid synthase, the enzyme that catalyzes the rate-limiting step of heme synthesis. Inhibition of this step can result in sideroblastic anemia.

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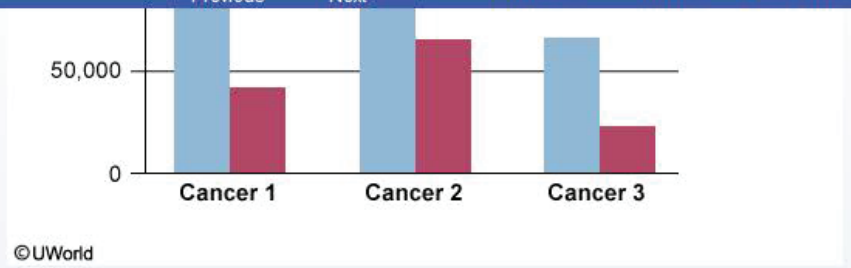
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affecting women in the United States, based on the American Cancer Society's *Cancer Facts & Figures 2019*. The x-axis lists the specific cancers, and the y-axis shows the projected number of patients affected.



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Which of the following lists of cancers most likely corresponds to Cancers 1, 2, and 3, respectively?

- A. Breast, lung, colorectal (77%)
- B. Lung, breast, colorectal (10%)
- C. Breast, ovary, lung (4%)
- D. Lung, breast, cervix (3%)
- E. Breast, colorectal, lung (4%)

Correct

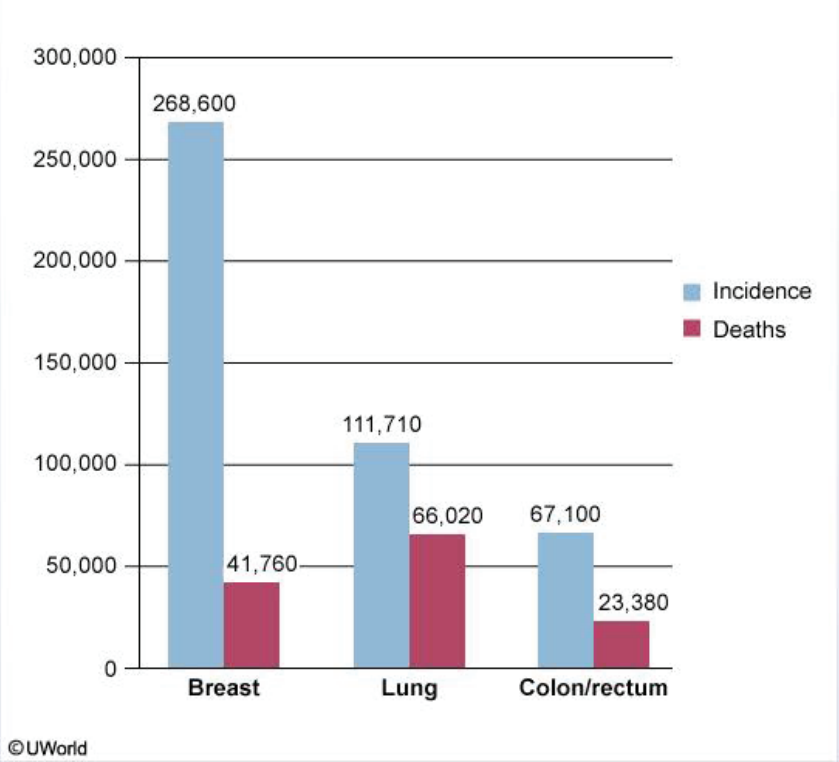
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According to estimates by the American Cancer Society, the most common cancers (excluding basal and

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According to estimates by the American Cancer Society, the most common cancers (excluding basal and squamous cell skin cancer) in 2019 among women living in the United States are (by order of incidence) breast, lung, and colorectal cancer. Although **breast cancer** has the **highest incidence** (268,600), its mortality is relatively low (41,760) due to early detection while the tumor is still localized. In contrast, the incidence of **lung cancer** in women is lower (111,710), but its **mortality is higher** (66,020), in part because lung cancer tends to be detected later and is less localized **(Choice B)**. Lung cancer has emerged as the leading cause of cancer mortality in women.

(Choices C and D) The incidence of ovarian (22,530) and cervical (13,170) cancers is much lower than that of the three cancers presented in the figure.

(Choice E) The incidence (67,100) and mortality (23,380) of colorectal cancer are lower than that of either breast or lung cancer.

Educational objective:
According to 2019 estimates, the most common cancers (excluding basal and squamous cell skin cancer) in women by order of incidence are breast, lung, and colorectal cancer. In terms of mortality, lung cancer claims the most lives, followed by breast and colorectal cancer.

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According to 2019 estimates, the most common cancers (excluding basal and squamous cell skin cancer) in women by order of incidence are breast, lung, and colorectal cancer. In terms of mortality, lung cancer claims the most lives, followed by breast and colorectal cancer.

References

- Cancer statistics, 2019.

Biostatistics	Hematology & Oncology	Prevalence and incidence
Subject	System	Topic

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A 45-year-old man comes to the office for progressive weakness and fatigue over the last year. The patient was adopted and does not know his family history. After a comprehensive physical examination and laboratory evaluation, the patient undergoes genetic testing. A loss of expression mutation is identified in a gene coding for a protein found on the basolateral surface of hepatocytes and enterocytes. The protein is known to interact with the transferrin receptor. Which of the following conditions is this patient at greatest risk of developing?

A. ~~Basal ganglia atrophy~~ (4%)
B. ~~Fat malabsorption and osteoporosis~~ (1%)
C. Iron deficiency anemia (39%)
✓ D. Liver cirrhosis and hepatocellular carcinoma (52%)
E. Pulmonary emphysema (1%)

Correct

52%
Answered correctly

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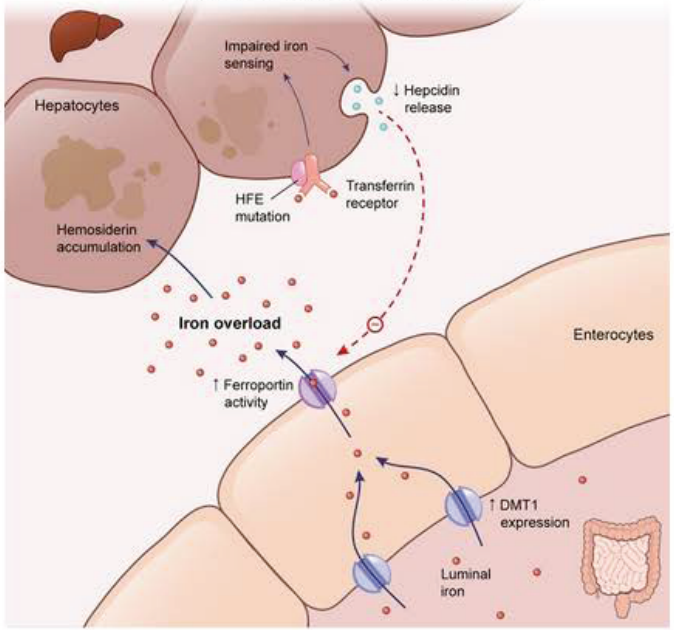
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Exhibit Display

HFE protein mutations and hemochromatosis



DMT1 = divalent metal transporter 1.
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Primary hemochromatosis (ie, hereditary hemochromatosis) is most commonly caused by mutations affecting the **HFE protein**. This protein normally interacts with the transferrin receptor to form a complex that functions as a sensor of iron stores. Mutations that inactivate the HFE protein cause enterocytes and hepatocytes to **detect falsely low iron levels**. This increases iron accumulation in the body through the following 2 mechanisms:

1. **Enterocytes** respond by increasing apical expression of divalent metal transporter 1 (DMT1), increasing iron absorption from the intestinal lumen
2. **Hepatocytes** respond by decreasing hepcidin synthesis; low hepcidin levels result in increased ferroportin expression on the basolateral surface of enterocytes. This allows increased iron secretion into the circulation, leading to iron overload

When body iron levels exceed 20 g, patients typically develop the classic triad of **micronodular cirrhosis**, diabetes mellitus, and skin pigmentation (ie, "bronze diabetes"). These patients are at an increased risk for **hepatocellular carcinoma**, congestive heart failure, and testicular atrophy/hypogonadism.

(Choice A) Basal ganglia atrophy is a potential complication commonly seen in Wilson disease (ie, hepatolenticular degeneration).

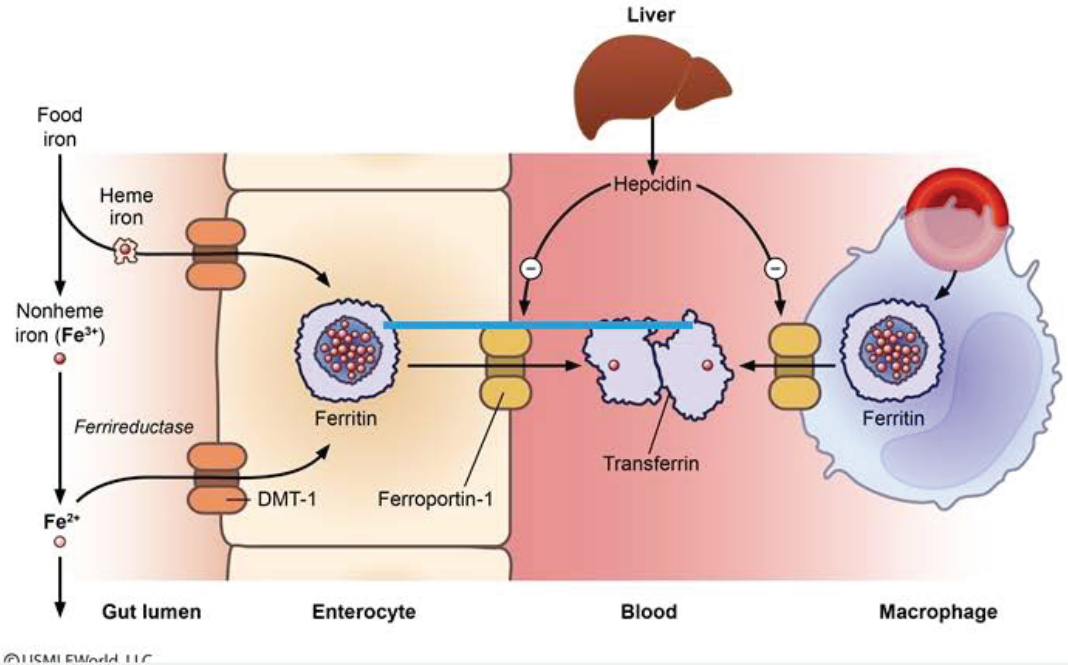
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Hepcidin and body iron regulation



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diabetes mellitus, and skin pigmentation (ie, "bronze diabetes"). These patients are at an increased risk for **hepatocellular carcinoma**, congestive heart failure, and testicular atrophy/hypogonadism.

(Choice A) Basal ganglia atrophy is a potential complication commonly seen in Wilson disease (ie, hepatolenticular degeneration).

(Choice B) Exocrine pancreatic function is usually preserved in patients with hemochromatosis. Therefore, fat malabsorption and osteoporosis (due to decreased vitamin D) would not typically be seen.

(Choice C) Iron deficiency anemia is a potential complication of blood loss, lack of dietary iron, or an inability to absorb iron (eg, celiac disease). Hemochromatosis results in iron overload, not iron deficiency.

(Choice E) Pulmonary emphysema is a potential complication of alpha-1 antitrypsin deficiency.

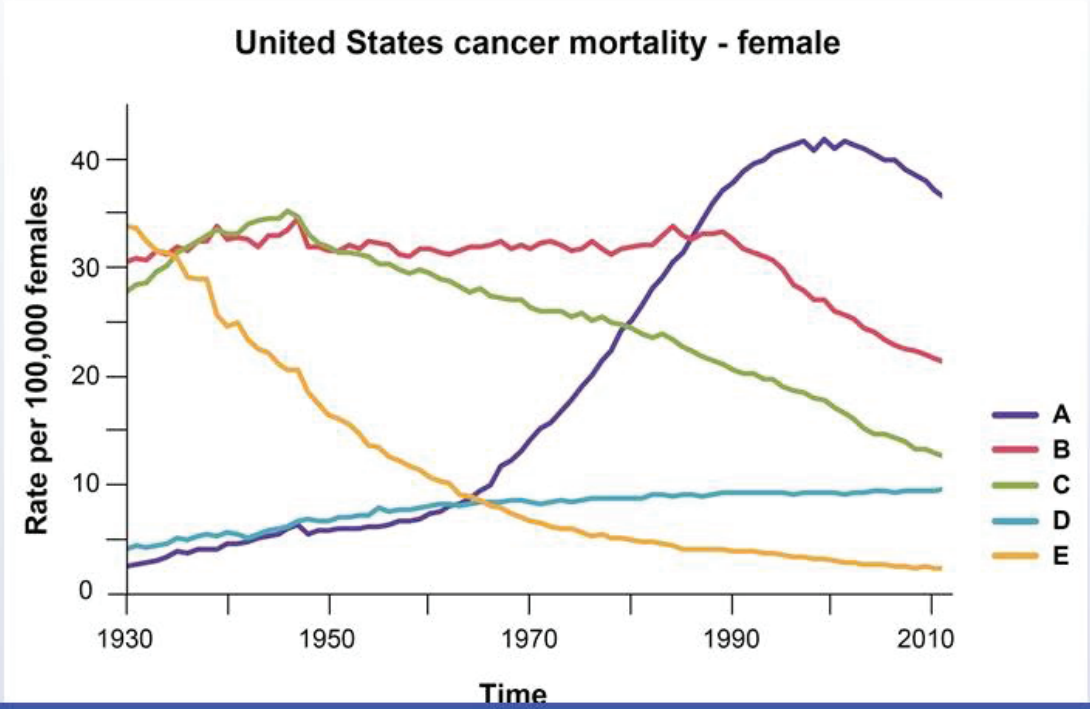
Educational objective:
HFE protein mutations are the most common cause of primary hemochromatosis. Inactivation of the HFE protein results in decreased hepcidin synthesis by hepatocytes and increased DMT1 expression by enterocytes, leading to iron overload. Patients with hemochromatosis are at an increased risk for liver cirrhosis and hepatocellular carcinoma.

References

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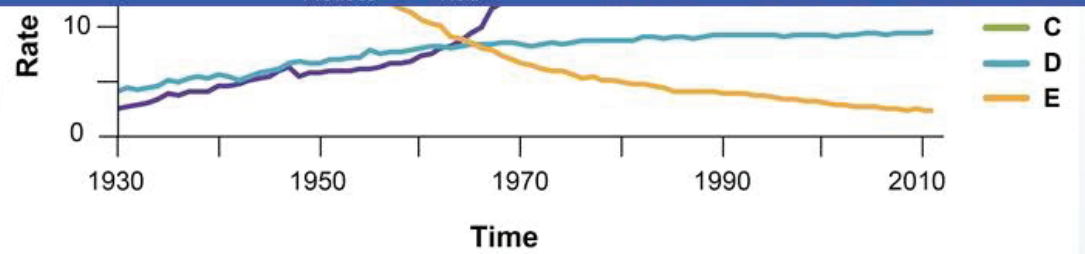
The age-adjusted mortality trends for 5 cancers in women in the United States are shown in the graph below.



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Which of the following curves best corresponds to lung cancer?

- A. A (78%)
- B. B (12%)
- C. C (3%)
- D. D (5%)
- E. E (0%)

Correct

78% Answered correctly

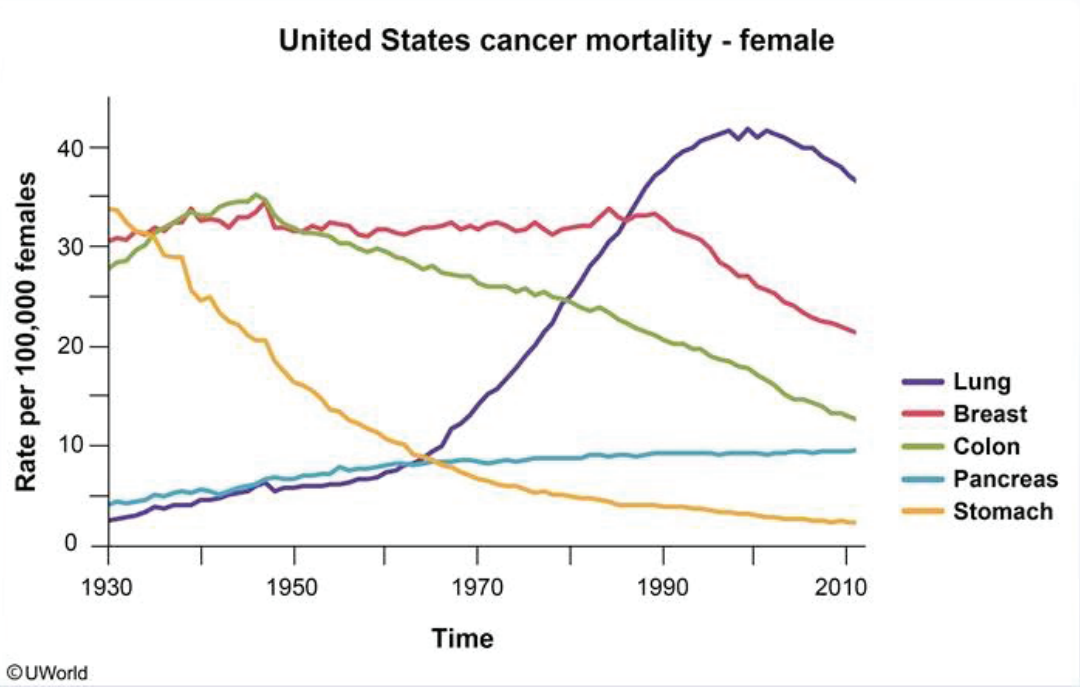
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Lung cancer has been the leading cause of **cancer mortality** in both **women** and men in the United States since the 1980s. **Tobacco use** (primary and secondhand) is the most important cause of lung cancer, particularly **non-small cell** lung cancer. Female use of cigarettes peaked in 1955, and mortality

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Lung cancer has been the leading cause of **cancer mortality** in both **women** and men in the United States since the 1980s. **Tobacco use** (primary and secondhand) is the most important cause of lung cancer, particularly **non-small cell** lung cancer. Female use of cigarettes peaked in 1955, and mortality rates increased 20-50 years after smoking onset. Lung cancer mortality began to decrease after 2000, corresponding to a decline in tobacco use.

Tobacco is a causative factor for numerous other cancers (eg, leukemia, nasopharyngeal, larynx, esophagus, pancreas, cervix, colon). It is directly carcinogenic to tissue by causing irritation and inflammation of the body's natural protective barriers. Patient education about tobacco's harmful effects is extremely important, as smoking cessation for even longtime users can be beneficial for reducing cancer risk and improving life expectancy.

(Choice B) Breast cancer is the most common non-skin cancer and the second most common cause of cancer death among women in the United States. Mortality from breast cancer began to decrease in the 1990s. Increased use of adjuvant chemotherapy and/or radiation and more frequent breast cancer screening are likely contributing factors to this decline.

(Choice C) Colon cancer mortality has decreased since the 1950s due to advances in surgical technique and adjuvant chemotherapy. Additional protective factors may include colorectal cancer screening,

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Exhibit Display

Cancer in United States populations: 2008-2012

	Highest incidence	Highest mortality
Female	1. Breast 2. Lung 3. Colon 4. Uterus 5. Thyroid	1. Lung 2. Breast 3. Colon 4. Pancreas 5. Ovary
Male	1. Prostate 2. Lung 3. Colon 4. Bladder 5. Melanoma	1. Lung 2. Prostate 3. Colon 4. Pancreas 5. Bladder

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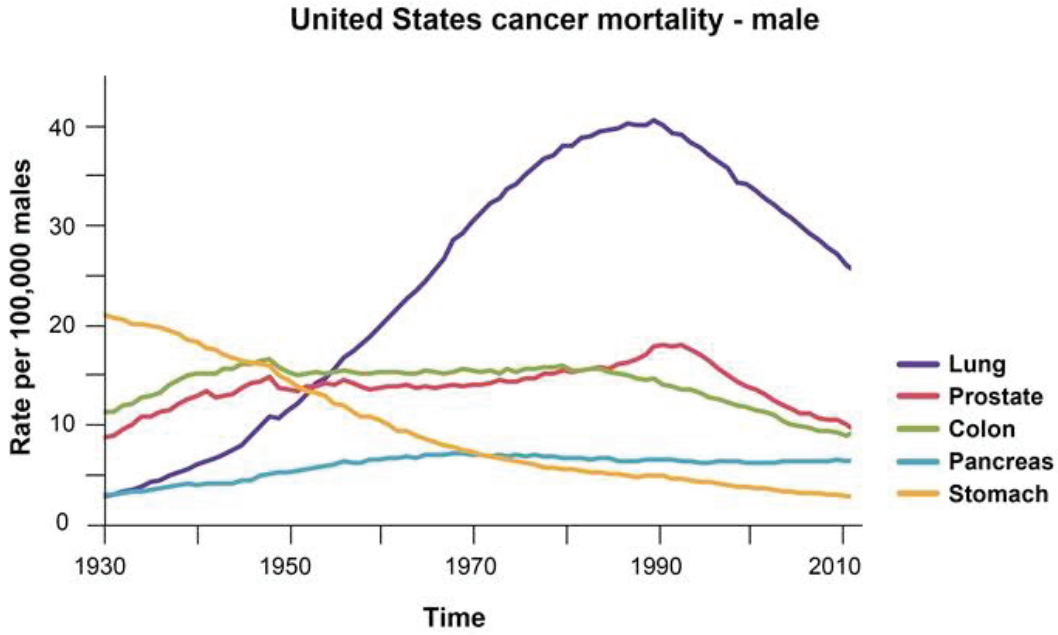
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(Choice B) Breast cancer is the most common non-skin cancer and the second most common cause of cancer death among women in the United States. Mortality from breast cancer began to decrease in the 1990s. Increased use of adjuvant chemotherapy and/or radiation and more frequent breast cancer screening are likely contributing factors to this decline.

(Choice C) Colon cancer mortality has decreased since the 1950s due to advances in surgical technique and adjuvant chemotherapy. Additional protective factors may include colorectal cancer screening, menopausal hormone therapy in women, and aspirin use.

(Choice D) The incidence and mortality of pancreatic cancer have increased in women over the last century and recently became the fourth most common cause of cancer death in women. Pancreatic cancer trends, like those of lung cancer, follow the pattern of increased smoking in women. However, lung cancer is responsible for three times more deaths than pancreatic cancer in women.

(Choice E) Stomach cancer incidence and mortality decreased drastically over the first half of the twentieth century. Proposed reasons include advances in refrigeration and food preservation (leading to decreased salt intake), and better sanitation and more adequate housing (reducing *Helicobacter pylori* infection rates).

Educational objective:

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and adjuvant chemotherapy. Additional protective factors may include colorectal cancer screening, menopausal hormone therapy in women, and aspirin use.

(Choice D) The incidence and mortality of pancreatic cancer have increased in women over the last century and recently became the fourth most common cause of cancer death in women. Pancreatic cancer trends, like those of lung cancer, follow the pattern of increased smoking in women. However, lung cancer is responsible for three times more deaths than pancreatic cancer in women.

(Choice E) Stomach cancer incidence and mortality decreased drastically over the first half of the twentieth century. Proposed reasons include advances in refrigeration and food preservation (leading to decreased salt intake), and better sanitation and more adequate housing (reducing *Helicobacter pylori* infection rates).

Educational objective:
Between 1950 and 2000, rising rates of tobacco use resulted in an increase in female lung cancer incidence and mortality. Lung cancer is currently the most common cause of cancer death in both women and men in the United States.

References

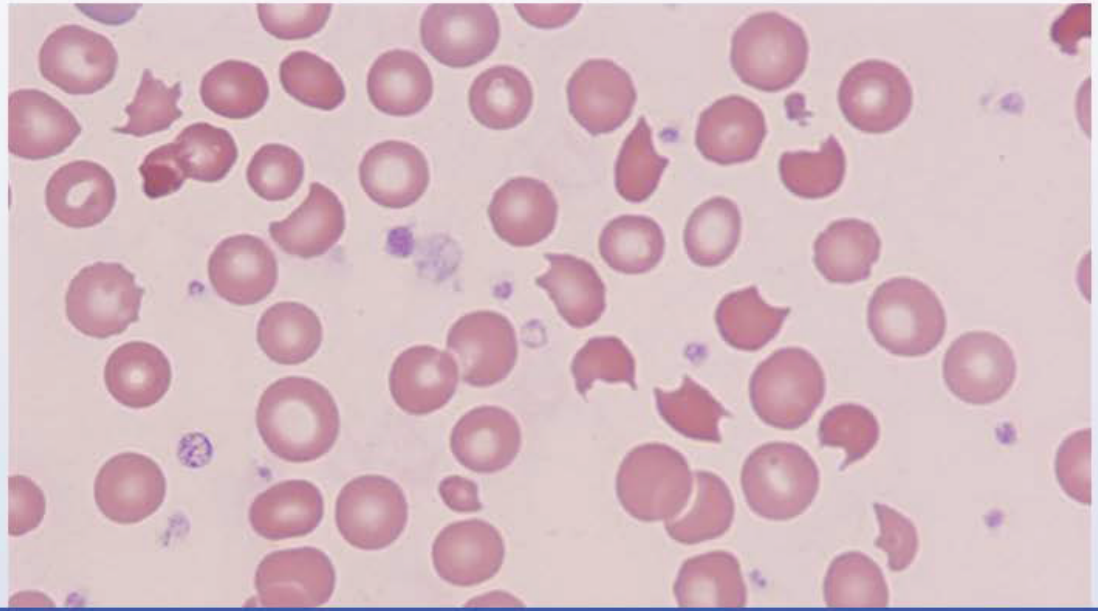
- Lung cancer incidence trends among men and women--United States, 2005-2009.

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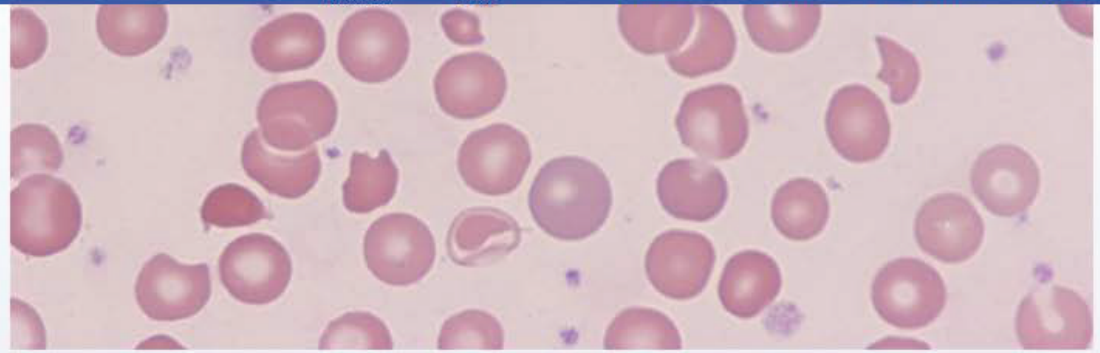
A 7-year-old boy comes to the office for follow-up. A week ago, the patient began having episodes of bloody diarrhea that have since resolved. His current laboratory studies show elevated blood urea nitrogen and serum creatinine levels. Complete blood count reveals anemia and thrombocytopenia. Coagulation studies are within normal limits. His peripheral blood smear is shown in the image below.



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Which of the following is the most likely cause of this patient's anemia?

A. Autoimmune hemolytic anemia (6%)

B. ~~Erythropoietin deficiency~~ (0%)

C. ~~Hemolytic anemia due to oxidative stress~~ (14%)

D. ~~Bone marrow fibrosis~~ (0%)

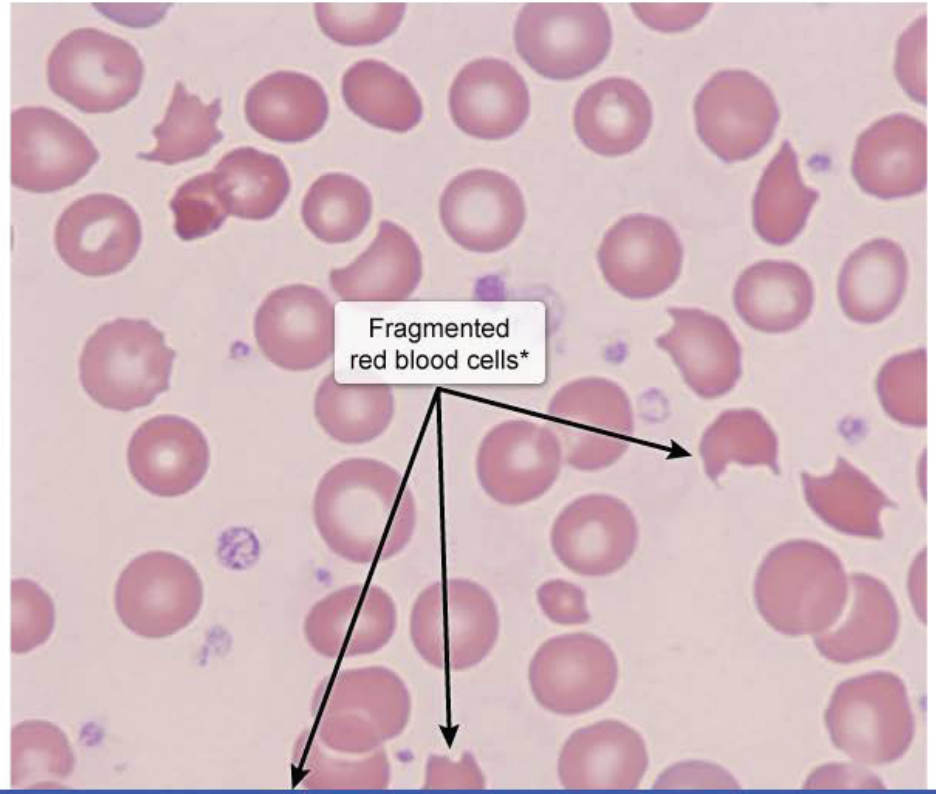
✓ E. Microangiopathic hemolytic anemia (77%)

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Schistocytes



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*Associated with microangiopathic hemolytic anemia and prosthetic heart valves

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The clinical presentation and the peripheral blood smear shown are typical of hemolytic uremic syndrome (HUS). Most cases of childhood HUS are preceded by **bloody diarrhea**, often caused by Shiga-like toxin released from enterohemorrhagic *Escherichia coli* (particularly strain O157:H7). Undercooked ground beef is a common cause of HUS.

The smear contains classic **schistocytes** (fragmented red cells) and few platelets. Schistocytes are diagnostic of a traumatic mechanism and indicate either **microangiopathic hemolytic anemia** (eg, HUS, thrombotic thrombocytopenic purpura [TTP], disseminated intravascular coagulation [DIC]) or mechanical damage (eg, prosthetic valve, severely calcified valves). HUS and TTP lie on a spectrum. Unlike in DIC, the coagulation system is not activated in HUS-TTP; therefore, coagulation studies (prothrombin time and partial thromboplastin time) are normal, as seen with this patient.

(Choice A) Autoimmune hemolytic anemia (AIHA) is due to an altered immune response and the production of antibodies against erythrocytes. AIHA can occur following infections with *Mycoplasma pneumoniae* and Epstein-Barr virus but not usually following a diarrheal illness. In addition, thrombocytopenia and renal failure are not associated with AIHA.

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Exhibit Display

Hemolytic uremic syndrome	
Pathogenesis	• Initial insult from Shiga toxin (*Escherichia coli* serotype O157:H7) • Vascular damage & microthrombi formation
Clinical features	• Preceding bloody diarrhea • Fatigue, pallor • Bruising, petechiae • Oliguria, edema
Laboratory findings	• Hemolytic anemia (schistocytes, ↑ bilirubin) • Thrombocytopenia • Acute kidney injury (↑ BUN, ↑ creatinine)
Treatment	• Fluid & electrolyte management • Blood transfusions • Dialysis

BUN = blood urea nitrogen.

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(HUS). Most cases
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The smear contains
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(Choice B) Erythropoietin deficiency results in normocytic, normochromic anemia; neither schistocytes nor decreased platelets are present. In addition, erythropoietin deficiency is usually seen in chronic renal failure; this patient has acute renal failure.

(Choice C) Glucose-6-phosphate dehydrogenase (G6PD) deficiency causes hemolytic anemia due to oxidative stress. It is not associated with thrombocytopenia or renal failure. The peripheral smear usually shows bite cells.

(Choice D) Leukoerythroblastic peripheral smears (ie, nucleated red cells and immature white cells) are usually seen when the marrow is replaced with fibrosis (or metastatic cancer). The red cells can be squeezed while passing through fibrous strands and appear on the peripheral smear as characteristic teardrop cells.

Educational objective:
Schistocytes suggest microangiopathic hemolytic anemia (eg, hemolytic-uremic syndrome [HUS], thrombotic thrombocytopenic purpura [TTP], disseminated intravascular coagulation [DIC]) or mechanical damage [eg, prosthetic valve]). In childhood, HUS is often preceded by bloody diarrhea. Coagulation studies (prothrombin time and partial thromboplastin time) are normal in HUS-TTP but abnormal in DIC.

References

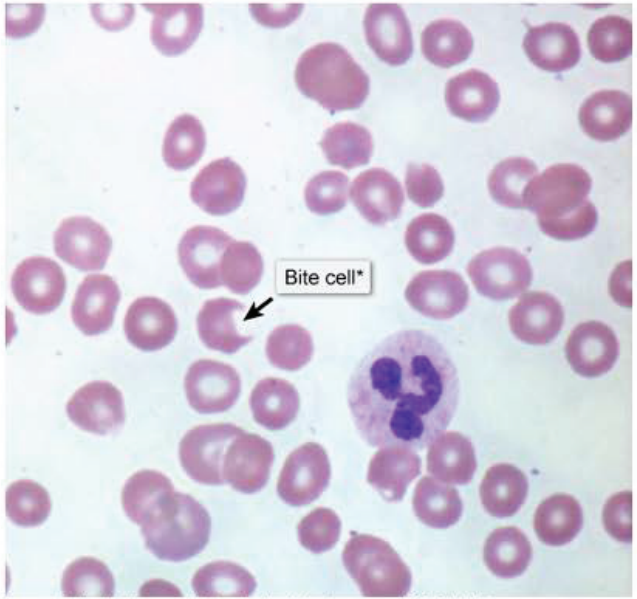
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Exhibit Display

Bite cells



*Associated with glucose-6-phosphate dehydrogenase (G6PD) deficiency

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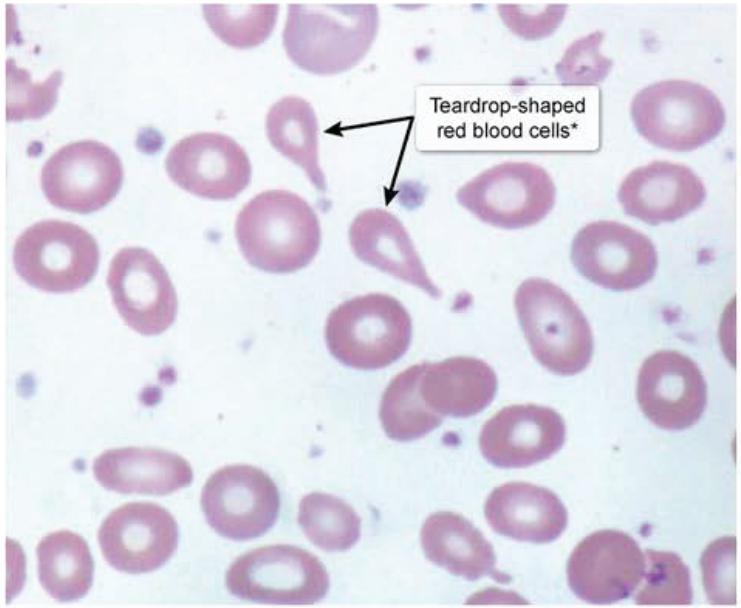
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Exhibit Display

Teardrop cells



* Associated with bone marrow infiltrative process (eg, fibrosis, metastasis)

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A 14-year-old girl comes to the emergency department due to rapidly progressive exertional dyspnea and generalized weakness, which were preceded by a mild febrile illness several days ago. She has a history of sickle cell disease and takes a daily folic acid supplement. Her temperature is 37.2 C (99.1 F), blood pressure is 115/70 mm Hg, and pulse is 112/min and regular. On examination, the patient has conjunctival pallor but no icterus. A cardiac flow murmur is present. The abdomen is soft and nontender with no organomegaly. Laboratory studies show a hematocrit of 16% with reticulocyte count of 0.1% (normal range, 0.5%-1.5%). Leukocyte and platelet counts are normal. Which of the following best describes the virus most likely responsible for this patient's current condition?

A. Enveloped double-stranded DNA virus (10%)
B. Enveloped negative-sense RNA virus (6%)
C. Enveloped positive-sense RNA virus (8%)
D. Nonenveloped double-stranded DNA virus (11%)
E. Nonenveloped positive-sense RNA virus (6%)
F. Nonenveloped single-stranded DNA virus (56%)

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This patient has developed severe anemia (eg, pallor, low hematocrit, flow murmur) following a minor febrile illness. If her bone marrow were able to respond appropriately to the degree of anemia, the reticulocyte count would be elevated (normal reticulocyte count is 0.5%-1.5% of red cells). Instead, the patient's reticulocyte count is markedly reduced.

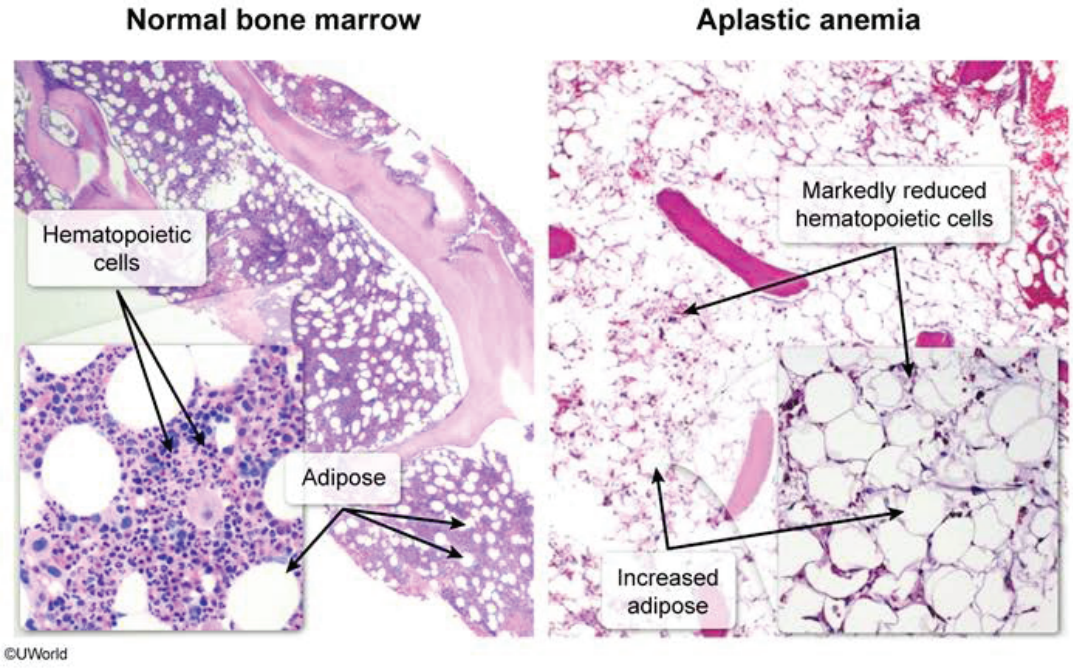
This scenario describes an **aplastic crisis**, which in sickle cell patients is usually due to **parvovirus B19** infection of erythroid precursor cells in the **bone marrow**. Parvovirus is a nonenveloped single-stranded DNA virus. **Destruction of the erythroid precursor cells** by this virus diminishes the number of reticulocytes available to replace the deformed and/or removed erythrocytes.

(Choices A, C, and E) Epstein-Barr virus (enveloped double-stranded DNA virus), hepatitis C virus (enveloped single-stranded positive-sense RNA virus), and hepatitis E virus (nonenveloped single-stranded positive-sense RNA virus) can cause hematopoietic depression and some measure of aplastic anemia (a cause of pancytopenia that should not be confused with aplastic crisis, which is limited to affecting erythrocytes). Anemia with normal leukocyte and platelet counts is more likely to occur with parvovirus B19 due to the virus's predilection for infecting proerythroblasts.

(Choice B) Important enveloped negative-sense RNA viruses include orthomyxoviruses (eg, influenza),

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cause of pancytopenia that should not be confused with aplastic crisis, which is limited to affecting erythrocytes). Anemia with normal leukocyte and platelet counts is more likely to occur with parvovirus B19 due to the virus's predilection for infecting proerythroblasts.

(Choice B) Important enveloped negative-sense RNA viruses include orthomyxoviruses (eg, influenza), paramyxoviruses (eg, measles and mumps), and rhabdoviruses (eg, rabies). However, these viruses are not known to infect erythroid progenitor cells in sufficient numbers to significantly impact erythropoiesis.

(Choice D) Nonenveloped double-stranded DNA viruses include adenoviruses, papillomaviruses, and polyomaviruses, which are not commonly known to cause hematopoietic depression or aplastic crisis.

Educational objective:
In patients with sickle cell anemia and other chronic hemolytic disorders, the most common viral cause of an aplastic crisis is infection of erythroid progenitor cells with parvovirus B19, a nonenveloped single-stranded DNA virus.

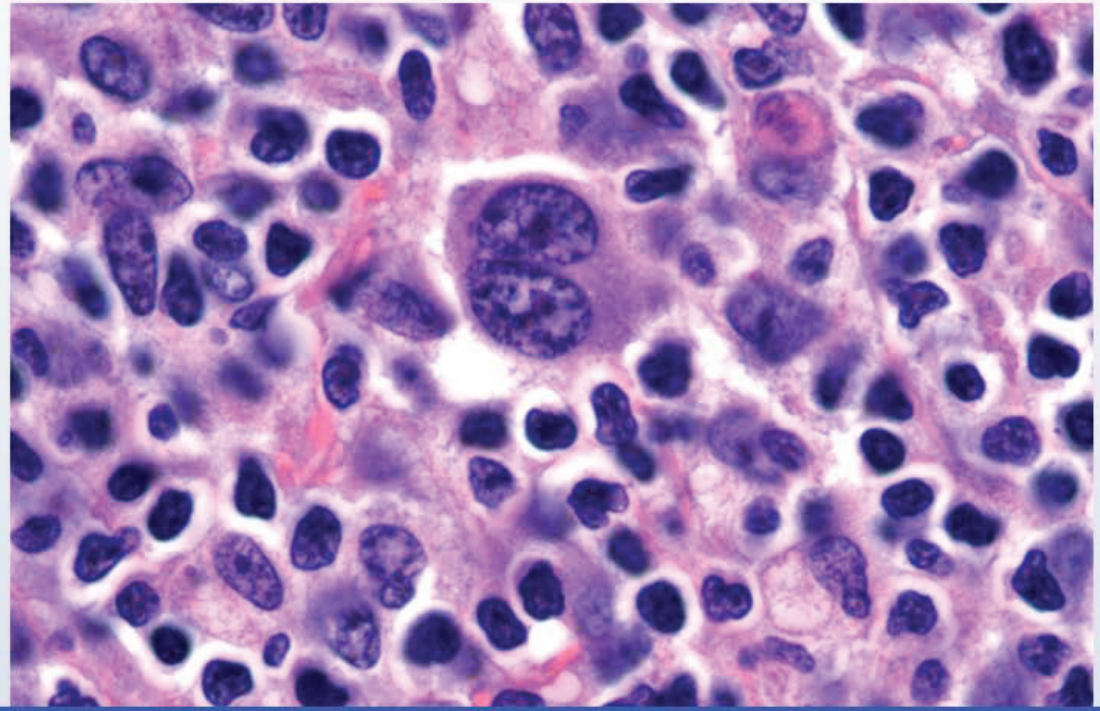
Microbiology	Hematology & Oncology	Sickle cell
Subject	System	Topic

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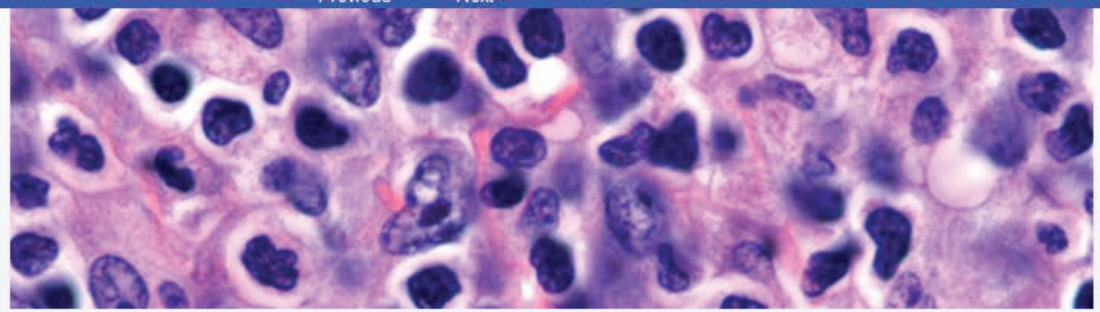
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A 46-year-old smoker presents to your office with a three week history of low-grade fever, weakness and neck swelling. Biopsy of the affected tissue reveals the following histologic findings:



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An abnormality in which of the following tissues is most likely responsible for this patient's symptoms?

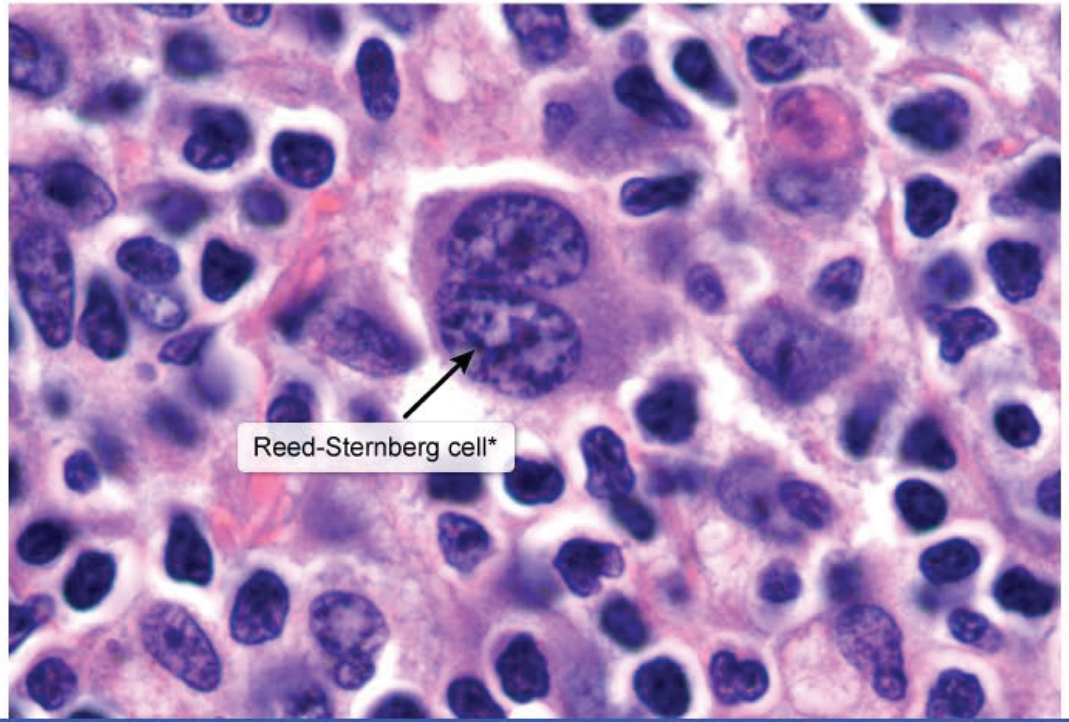
A. Respiratory epithelium (6%)
B. Thyroid gland (7%)
C. Lymphoid tissue (78%)
D. Myeloid precursors (7%)
E. Skin epithelium (0%)

78%
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01/30/2021

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Hodgkin lymphoma



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In order to answer this question, you must be able to recognize the characteristic histology. The tissue biopsy shows numerous lymphocytes (small cells with dark, round nuclei and a small rim of cytoplasm), meaning that it was most likely taken from a lymph node. The key finding is the giant binucleated cell, a Reed-Sternberg (RS) cell, in the center of the slide. RS cells are derived from germinal center B-lymphocytes and are the neoplastic cells of Hodgkin lymphoma (HL). RS cells must be present in order to make the diagnosis of HL. The two mirror-image nuclei of RS cells are often described as having the appearance of "owl's eyes."

(Choice A) The respiratory epithelium is a pseudostratified columnar ciliated epithelium that extends down to the level of the bronchioles. At the bronchioles, the epithelium gradually becomes cuboidal and then transitions to a flat, single-celled alveolar lining of Type I pneumocytes.

(Choice B) A goiter may cause neck swelling. Histologically, Hashimoto thyroiditis has the appearance of lymphocytes infiltrating between thyroid follicles.

(Choice D) Reed-Sternberg cells are not associated with leukemia. The classic finding in patients with leukemia is a peripheral blood smear with leukemic cells, leukocytosis and thrombocytopenia.

(Choice E) Both melanoma and squamous cell carcinoma can metastasize from the skin causing lymphadenopathy. The cells on this tissue biopsy show no evidence of squamous or melanocytic

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transitions to a flat, single-celled alveolar lining of type I pneumocytes.

(Choice B) A goiter may cause neck swelling. Histologically, Hashimoto thyroiditis has the appearance of lymphocytes infiltrating between thyroid follicles.

(Choice D) Reed-Sternberg cells are not associated with leukemia. The classic finding in patients with leukemia is a peripheral blood smear with leukemic cells, leukocytosis and thrombocytopenia.

(Choice E) Both melanoma and squamous cell carcinoma can metastasize from the skin causing lymphadenopathy. The cells on this tissue biopsy show no evidence of squamous or melanocytic differentiation, however.

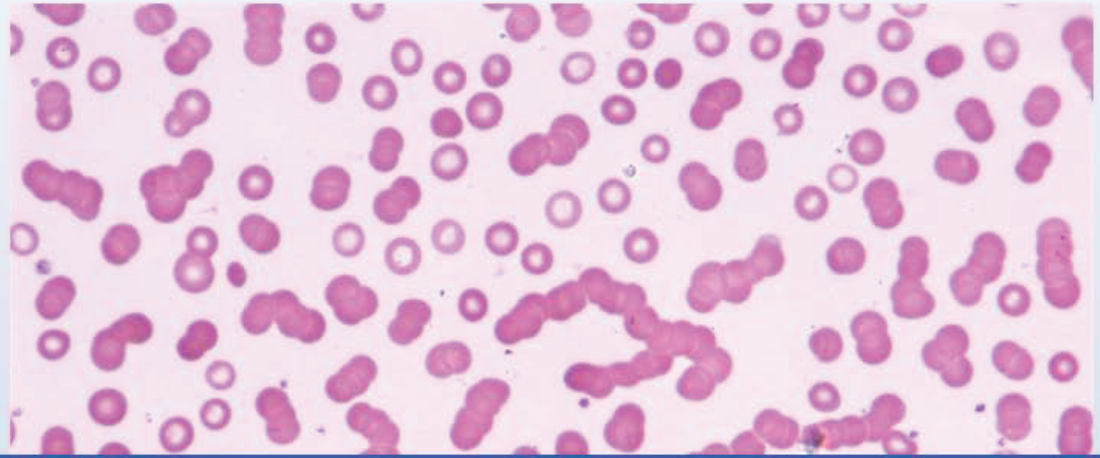
Educational Objective:
Reed-Sternberg cells are large binucleated cells with an "owl's eyes" appearance that appear on a background of lymphocytic infiltrates. Reed-Sternberg cells must be present histopathologically in order to make the diagnosis of Hodgkin lymphoma.

Pathology	Hematology & Oncology	Hodgkins lymphoma
Subject	System	Topic

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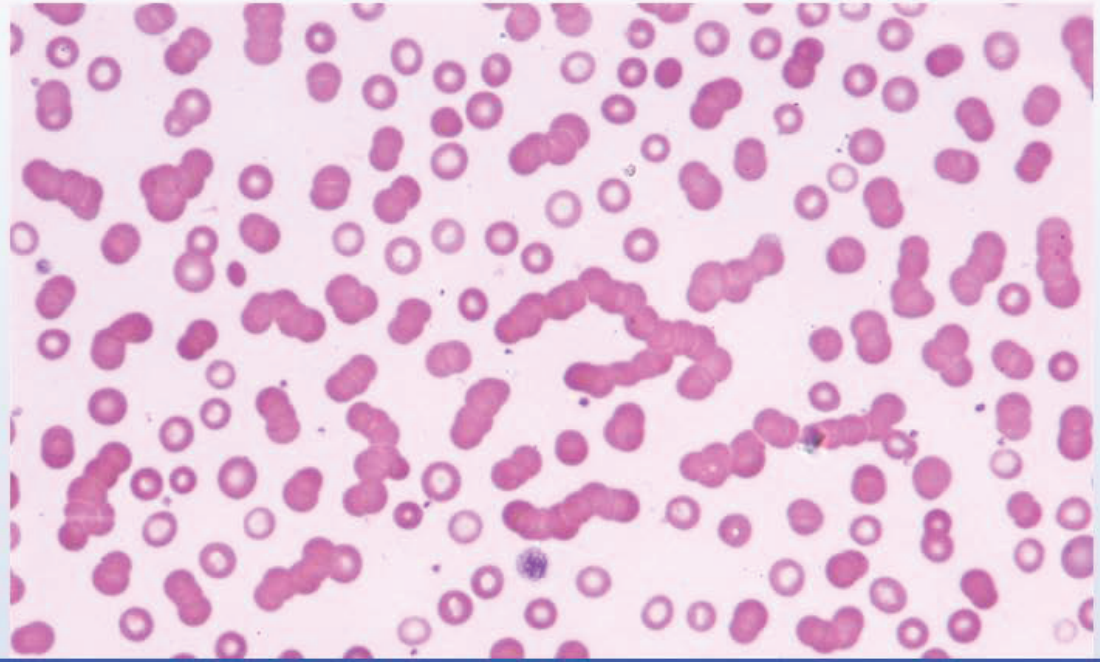
A 65-year-old man comes to the office due to 4 months of worsening fatigue. The patient feels tired with simple household chores. He has a 15-pack-year smoking history and drinks 2 or 3 beers daily. Temperature is 37 C (98.6 F), blood pressure is 134/86 mm Hg, and pulse is 76/min. Physical examination reveals a late systolic ejection murmur with a soft S2. The lungs are clear to auscultation. The abdomen is soft and nontender with no hepatosplenomegaly. There are no focal neurological deficits. Laboratory testing reveals hemoglobin is 9 g/dL and mean corpuscular volume is 93 μm^3. Peripheral blood smear is shown below:



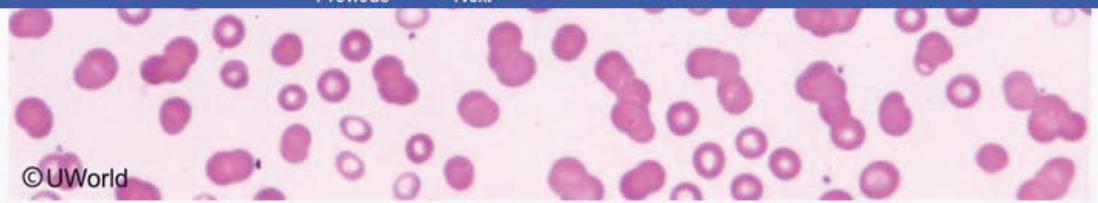
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Which of the following best explains the observed erythrocyte findings in this patient?

A. ~~Chronic gastrointestinal blood loss~~ (7%)

B. Excessive cold agglutinin production (22%)

C. Increased serum paraproteins (64%)

D. ~~Mechanical erythrocyte injury~~ (4%)

E. ~~Nutritional vitamin B_{12} deficiency~~ (2%)

Correct

64%
Answered correctly

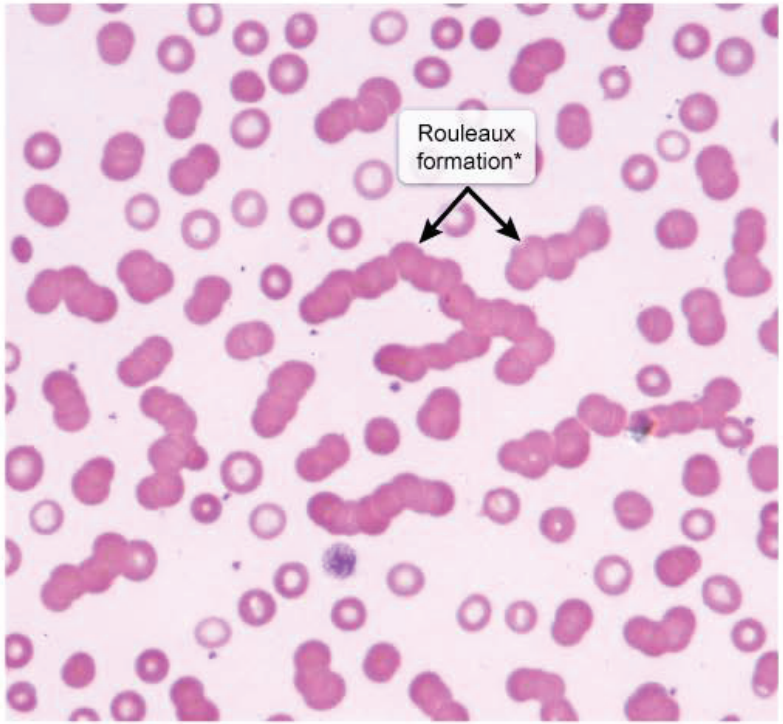
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Last Updated

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Multiple myeloma



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*Stacked erythrocytes due to increased protein (eg, immunoglobulin) in blood ©UWorld

This patient's peripheral blood smear shows rows of erythrocytes stacked on one another like coins (**rouleaux formation**). This occurs due to elevated levels of **circulating proteins**, which disrupts the repulsive electrostatic charge on the erythrocyte surface and causes **stacked aggregation**. Although rouleaux formation can be seen with inflammatory conditions (eg, infection, rheumatic disease) that increase acute-phase reactants (eg, fibrinogen), it is classically linked to lymphoproliferative/plasma cell disorders such as **multiple myeloma** and Waldenstrom macroglobulinemia, which generate high levels of **monoclonal paraprotein** (immunoglobulins).

Multiple myeloma is a plasma cell malignancy often associated with **normocytic anemia**, osteolytic bone lesions, and hypercalcemia due to proliferation of neoplastic cells in the bone marrow. Patients also frequently have renal insufficiency (due to immunoglobulin light-chain cast nephropathy) and nonspecific symptoms (eg, fatigue). Diagnosis is generally made using serum/urine protein electrophoresis (monoclonal M-spike) and bone marrow biopsy.

(Choice A) Chronic gastrointestinal blood loss is a leading cause of iron-deficiency anemia, which usually results in microcytosis and hypochromia on peripheral smear (sometimes with target cells). Rouleaux formation and normocytic erythrocytes would be atypical.

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(monoclonal M-spike) and bone marrow biopsy.

(Choice A) Chronic gastrointestinal blood loss is a leading cause of iron-deficiency anemia, which usually results in microcytosis and hypochromia on peripheral smear (sometimes with target cells). Rouleaux formation and normocytic erythrocytes would be atypical.

(Choice B) Cold agglutinins are cross-reactive IgM antibodies that form with some infections (particularly *Mycoplasma pneumoniae*) and hematologic malignancies. Cold agglutinins typically cause clumping agglutination (not stacked-coin agglutination) and hemolysis.

(Choice D) Mechanical erythrocyte injury is common in patients with damaged or artificial heart valves. Although this patient has a cardiac murmur that indicates possible aortic stenosis, mechanical erythrocyte injury is usually associated with schistocytes on peripheral blood smear, not rouleaux formation.

(Choice E) Vitamin B_{12} deficiency causes abnormal hematologic cell nuclear maturation, which leads to macrocytic anemia and hypersegmented neutrophils on peripheral blood smear.

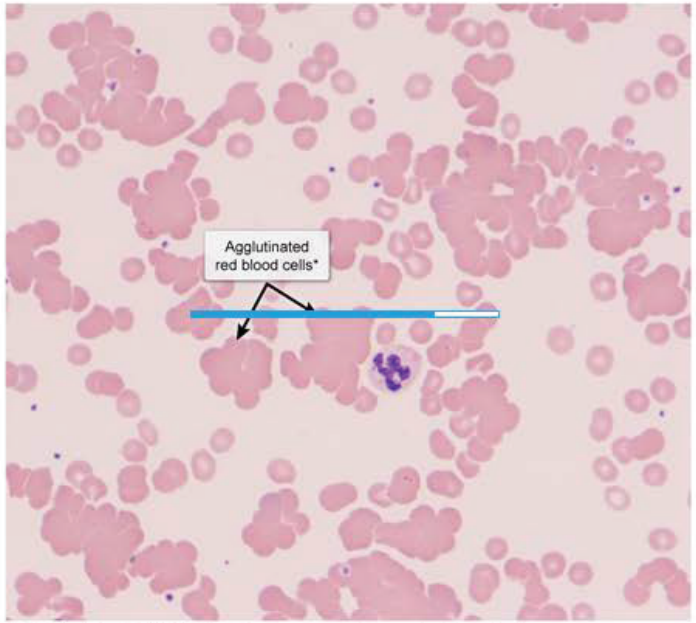
Educational objective:
Multiple myeloma is associated with elevated circulating paraproteins (monoclonal immunoglobulins), which causes erythrocytes to stack like coins (rouleaux formation). Patients classically have normocytic

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Cold agglutinin disease



*Red blood cells bound by IgM antibodies at low temperatures (ie, below core body temperature)

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(Choice E) Vitamin B_{12} deficiency causes abnormal hematologic cell nuclear maturation, which leads to macrocytic anemia and hypersegmented neutrophils on peripheral blood smear.

Educational objective:
Multiple myeloma is associated with elevated circulating paraproteins (monoclonal immunoglobulins), which causes erythrocytes to stack like coins (rouleaux formation). Patients classically have normocytic anemia, hypercalcemia, bone pain, and renal insufficiency.

Pathology	Hematology & Oncology	Multiple myeloma
Subject	System	Topic

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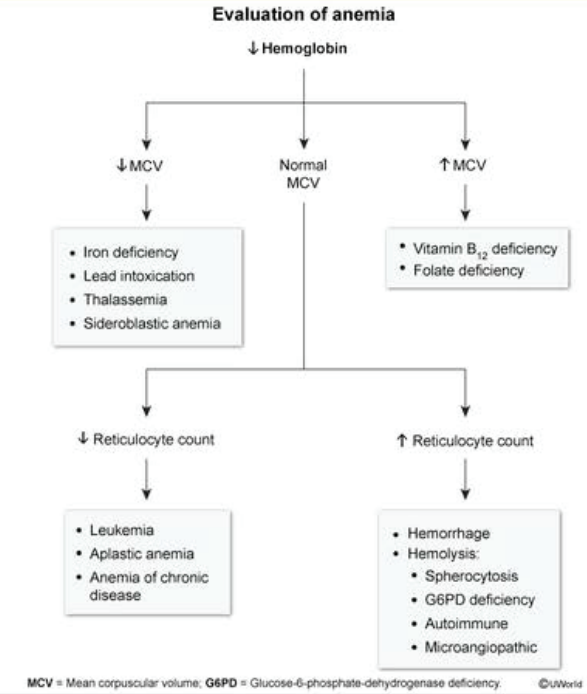
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A 16-year-old girl comes to the office due to fatigue for the past few months. She attends high school and plays on the school soccer team but says that her endurance has decreased. The patient sleeps 9 hours a night and has been a vegetarian for the past year. She reached menarche at age 13 and has had regular menses for the past 6 months. The patient is not sexually active and does not smoke cigarettes but does report drinking 1 or 2 cans of beer a month. Her blood pressure is 110/60 mm Hg, pulse is 70/min, and BMI is 21 kg/m^2. Physical examination shows a well-nourished teenage girl with pale conjunctivae. Her hemoglobin is 9.2 g/dL. Which of the following sets of additional laboratory findings are most likely to be seen in this patient?

	Serum ferritin	Circulating transferrin	Mean corpuscular volume	Hypersegmented neutrophils	Serum folate	
A.	~~Normal~~	~~Normal~~	~~74~~	~~None~~	~~Normal~~	(1%)
✓ B.	~~Low~~	~~High~~	~~76~~	~~None~~	~~Normal~~	(54%)
C.	~~Low~~	~~Low~~	~~84~~	~~None~~	~~Normal~~	(6%)

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• Aplastic anemia • Hemolysis:

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MCV = Mean corpuscular volume; **G6PD** = Glucose-6-phosphate-dehydrogenase deficiency. ©UWorld

This girl has fatigue and conjunctival pallor, which are suggestive of anemia. The diagnosis is confirmed by her low hemoglobin. Women of **childbearing age** are at risk for **iron-deficiency anemia** due to menstrual cycle blood loss, especially teenage girls who have higher iron requirements due to growth. In this patient, decreased consumption of dietary iron (eg, vegetarianism) is an additional risk factor. As iron deficiency develops, the following sequence can be seen with laboratory testing:

1. Decreased bone marrow iron stores (ferritin and hemosiderin)
2. **Decreased serum ferritin**
3. Increased serum total iron-binding capacity, reflecting **increased transferrin**
4. Decreased serum iron concentration
5. Decreased hemoglobin
6. Appearance of microcytic, hypochromic red blood cells (low mean corpuscular volume/mean corpuscular hemoglobin [MCV/MCH])

Ferritin is an intracellular iron-storage protein that is used as a serum marker of total body iron stores. It is decreased in iron deficiency and elevated in iron overload or during infection/inflammation (acute phase reaction). Transferrin transports iron through the plasma. When iron levels are normal, approximately one

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corpuscular hemoglobin [MCV/MCH])

Ferritin is an intracellular iron-storage protein that is used as a serum marker of total body iron stores. It is decreased in iron deficiency and elevated in iron overload or during infection/inflammation (acute phase reaction). Transferrin transports iron through the plasma. When iron levels are normal, approximately one third of circulating transferrin is bound to iron. In iron deficiency, hepatic synthesis of transferrin increases but transferrin saturation drops due to decreased release of iron into the plasma from intracellular stores.

(Choice A) The earliest signs of iron deficiency are low serum ferritin and high serum transferrin, which manifest before overt anemia develops. This pattern of findings is more consistent with α- or β-thalassemia, which usually cause microcytic anemia with normal ferritin and transferrin levels.

(Choice C) Circulating transferrin levels would increase and MCV would decrease in a patient with iron-deficiency anemia.

(Choice D) Low hemoglobin in the setting of a normal MCV, low circulating transferrin, and high serum ferritin is suggestive of anemia of chronic disease, which is often associated with infections and inflammatory conditions. Other acute phase reactants (eg, C-reactive protein, sedimentation rate) are usually elevated in these patients.

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(Choice D) Low hemoglobin in the setting of a normal MCV, low circulating transferrin, and high serum ferritin is suggestive of anemia of chronic disease, which is often associated with infections and inflammatory conditions. Other acute phase reactants (eg, C-reactive protein, sedimentation rate) are usually elevated in these patients.

(Choices E and F) Hypersegmented neutrophils are characteristic of megaloblastic anemias, which can be caused by folate and vitamin B_{12} deficiency. Folate deficiency is unlikely in this patient, as folate is found in many vegetable products. Although vegetarians are at risk for vitamin B_{12} deficiency, depletion of hepatic B_{12} stores takes several years, and this patient has been a vegetarian only for the past year.

Educational objective:

Anemia in a woman of childbearing age is most commonly caused by iron deficiency secondary to menstrual blood loss. Iron deficiency is associated with decreased serum ferritin, increased total iron-binding capacity (transferrin), and microcytic, hypochromic red blood cells.

References

- Guideline for the laboratory diagnosis of functional iron deficiency.

Pathology Hematology & Oncology Iron deficiency anemia

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A 62-year-old man comes to the office due to worsening fatigue. The patient has long-standing type 2 diabetes mellitus complicated by nephropathy. Laboratory results are as follows:

Hemoglobin	9.4 g/dL
Mean corpuscular volume	90 μm^3
Platelets	200,000/mm^3
Leukocytes	7,500/mm^3
Serum creatinine	3.2 mg/dL
Total bilirubin	0.8 mg/dL
Serum ferritin	350 ng/mL
Transferrin saturation	30% (normal: 20%-50%)

After appropriate treatment is initiated for his anemia, which of the following changes is most likely to occur in this patient's erythroid cells?

A. Decrease in free protoporphyrin levels (26%)

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Total bilirubin	0.8 mg/dL
Serum ferritin	350 ng/mL
Transferrin saturation	30% (normal: 20%-50%)

After appropriate treatment is initiated for his anemia, which of the following changes is most likely to occur in this patient's erythroid cells?

A. Decrease in free protoporphyrin levels (26%)
B. Decrease in reticuloendothelial destruction (8%)
C. Increase in progenitor cell differentiation (57%)
D. Switch of hemoglobin to the fetal form (0%)
E. Synchronization of nuclear and cytoplasmic maturation (6%)

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Correct

57% Answered correctly

55 secs Time Spent

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Patients with **chronic kidney disease** (CKD) often develop **normocytic anemia** as the glomerular filtration rate worsens due to **inadequate production of erythropoietin** (EPO), a glycoprotein hormone produced by peritubular fibroblast cells in the renal cortex. EPO is released into the bloodstream in response to renal tissue hypoxia and subsequently acts on erythrocyte progenitor cells (erythroid colony–forming unit cells) in the bone marrow to reduce apoptosis and increase **differentiation** into mature red blood cells.

Although healthy individuals respond to anemia by increasing EPO levels up to 10,000-fold, patients with CKD have chronic inflammatory damage to renal EPO-producing cells and are often unable to generate sufficient levels of EPO to maintain adequate erythrocytosis. These individuals are often treated with **synthetic forms of EPO** (eg, epoetin, darbepoetin) to supplement intrinsic EPO production and stimulate erythropoiesis. Because synthetic forms of EPO can rapidly deplete iron stores (due to increased red blood cell production), patients should be tested for iron deficiency prior to treatment with these agents.

(Choice A) Protoporphyrins (heme precursors) are elevated in patients with iron deficiency anemia. Treatment of iron deficiency anemia (eg, iron supplementation) leads to the conversion of protoporphyrins to heme, thereby reducing free protoporphyrin levels. Patients with iron deficiency anemia usually have low serum ferritin levels and transferrin saturation.

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(Choice B) Warm autoimmune hemolytic anemia is characterized by antibodies against antigens on the red cell membrane that result in phagocytosis in the reticuloendothelial system (eg, spleen). Autoimmune hemolytic anemia is usually treated with immune-suppressing agents (eg, prednisone), which blunt antibody production and reduce red cell destruction. This patient with a normal bilirubin level is unlikely to have hemolytic anemia.

(Choice D) Sickle cell anemia is caused by mutations in the beta globin chain, which results in the polymerization of deoxygenated hemoglobin molecules ("sickling"). Treatment with hydroxyurea induces expression of fetal hemoglobin (which is unaffected by the sickle mutation) over adult hemoglobin, thereby preventing polymerization of hemoglobin molecules.

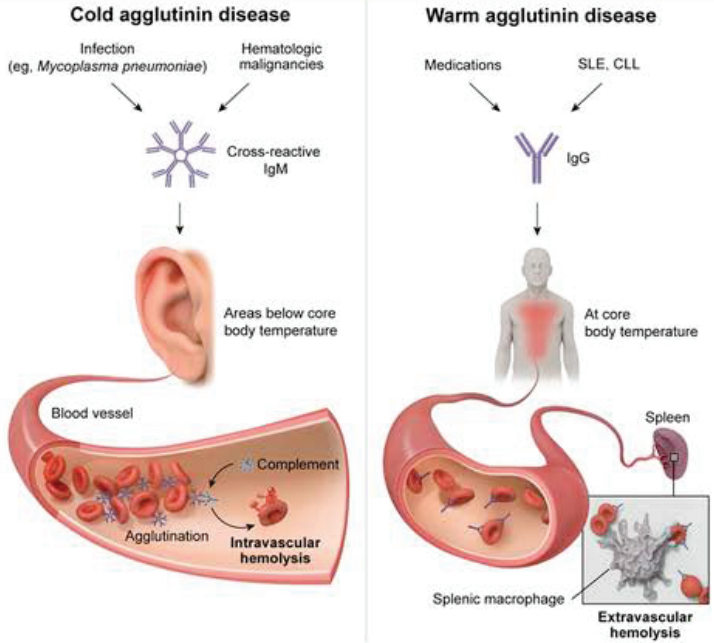
(Choice E) Deficiency of vitamin B_{12}/folate (megaloblastic anemia) impairs nucleic acid metabolism, which results in slowed production of erythrocyte precursors in the bone marrow. Replacement of vitamin B_{12}/folate corrects the anemia by improving nuclear maturation. Megaloblastic anemia is typically associated with macrocytic (elevated mean corpuscular volume) anemia.

Educational objective:
Erythropoietin (EPO) is produced by peritubular fibroblast cells in the renal cortex in response to decreased renal oxygen delivery. EPO acts on erythrocyte precursors in the bone marrow to increase red blood cell

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CLL = chronic lymphocytic leukemia; SLE = systemic lupus erythematosus.
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renal oxygen delivery. EPO acts on erythrocyte precursors in the bone marrow to increase red blood cell

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Educational objective:
Erythropoietin (EPO) is produced by peritubular fibroblast cells in the renal cortex in response to decreased renal oxygen delivery. EPO acts on erythrocyte precursors in the bone marrow to increase red blood cell production. Patients with chronic kidney disease often have damage to renal EPO-producing cells, which results in normocytic anemia.

References

- Renal erythropoietin-producing cells in health and disease.

Physiology Hematology & Oncology Erythropoietin

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A 64-year-old man comes to the office due to several weeks of worsening back pain, fatigue, and polyuria. Physical examination reveals mucosal pallor and diffuse bony tenderness. Laboratory studies are significant for normocytic anemia, hypercalcemia, and renal failure. Serum protein electrophoresis demonstrates a monoclonal spike in the gamma globulin region. Bone marrow biopsy shows a large number of abnormal plasma cells. Treatment with lenalidomide is started; this medication increases affinity of E3 ubiquitin ligase enzyme to substrate transcription factors. Which of the following is the most likely effect of this medication on these transcription factors?

A. Decreased cell surface expression (3%)
B. ~~Decreased lysosomal proteolysis~~ (5%)
C. ~~Increased binding to promoter region~~ (4%)
D. Increased intracellular degradation (85%)
E. Increased nuclear translocation (1%)

85% 02 mins, 12 secs 01/09/2021

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Multiple myeloma is a plasma cell neoplasm associated with the overproduction of **monoclonal immunoglobulins**. Proliferation of neoplastic plasma cells in the bone marrow often causes bone pain (eg, back pain), hypercalcemia (eg, polyuria), and osteolytic lesions; patients also frequently develop normocytic anemia and renal insufficiency. Treatment frequently includes medications that inhibit proteasome activity (eg, bortezomib) or increase ubiquitination of regulatory proteins produced in excess in neoplastic cells (eg, **lenalidomide**).

Lenalidomide is a derivative of thalidomide, an antiemetic agent used in pregnancy until significant teratogenic effects were identified. Lenalidomide increases the binding affinity of the **E3 ubiquitin ligase complex** to specific **transcription factors** (TFs) (eg, Ikaros and Aiolos 2 zinc finger transcription factors) that are overexpressed in myeloma cells. Binding attaches ubiquitin to the TFs, which leads to their subsequent **destruction by the proteasome**. Because these TFs are required for myeloma cell survival, diminished intracellular concentrations cause cell death. Other mature B-cell malignancies such as mantle cell lymphoma and myelodysplastic syndrome (some cases are caused by B-cell proliferation) also overexpress these TFs; therefore, lenalidomide is often effective against these neoplasms.

(Choice A) TFs are proteins that bind to a specific DNA sequence to increase or suppress its transcription to messenger RNA; they are not expressed on the cell surface.

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overexpress these TFs; therefore, lenalidomide is often effective against these neoplasms.

(Choice A) TFs are proteins that bind to a specific DNA sequence to increase or suppress its transcription to messenger RNA; they are not expressed on the cell surface.

(Choice B) Lysosomes are membrane-bound organelles with hydrolytic enzymes that break down molecules from outside the cell (via endocytosis) or within the cytoplasm (autophagy). Although lysosomes and proteasomes are the 2 major pathways of protein degradation in the cell, lysosomes digest proteins independent of ubiquitination; therefore, lenalidomide does not alter lysosome proteolysis.

(Choice C) Ubiquitin binding does not alter the way TFs interact with DNA; instead, it results in increased proteolysis of the TFs by proteasomes. In contrast, phosphorylation or acetylation can affect TF binding to promoter regions of DNA.

(Choice E) Proteins targeted for the nucleus have nuclear localization signals, short chains of amino acids that promote transport into the nucleus. These are added during protein synthesis in the endoplasmic reticulum; ubiquitination does not affect nuclear localization.

Educational objective:
Multiple myeloma is often treated with medications that block proteasome activity (eg, bortezomib) or increase ubiquitination of specific transcription factors (eg, lenalidomide). Lenalidomide increases E3

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Educational objective:

Multiple myeloma is often treated with medications that block proteasome activity (eg, bortezomib) or increase ubiquitination of specific transcription factors (eg, lenalidomide). Lenalidomide increases E3 ubiquitin ligase binding to transcription factors overexpressed in myeloma, which results in increased transcription factor destruction by the proteosome and subsequent cancer cell death.

References

- The novel mechanism of lenalidomide activity.

Pharmacology Hematology & Oncology Multiple myeloma

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A 5-year-old boy is brought to the emergency department due to 2 days of dark, low-volume urine and decreased energy. The parents say that the boy had abdominal pain, fever, and bloody diarrhea for 4 days, which resolved about 3 days ago without treatment. The day before the onset of symptoms, the patient swam in a lake and ate hamburgers at a family picnic. His vital signs are within normal limits. Physical examination shows pallor but is otherwise normal. He has no peripheral edema or rashes. Laboratory evaluation shows anemia, thrombocytopenia, and elevated blood urea nitrogen and serum creatinine. Which of the following findings is most likely to be seen in this patient?

A. Elevated haptoglobin level (9%)
B. Elevated serum indirect bilirubin (53%)
C. ~~Elevated thrombin and prothrombin time~~ (7%)
D. ~~Low fibrinogen and elevated D-dimer level~~ (14%)
E. ~~Positive Coombs test~~ (10%)
F. ~~Positive Streptozyme test~~ (4%)

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Hemolytic uremic syndrome	
Etiology	Shiga toxin-producing bacteria • *Escherichia coli* O157:H7 • *Shigella*
Clinical features	• Antecedent diarrheal illness (often bloody) • Hemolytic anemia with schistocytes • Thrombocytopenia • Acute kidney injury

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This patient has **hemolytic uremic syndrome (HUS)**, which is most often caused by infection with shiga toxin-producing organisms such as ***Escherichia coli* O157:H7** or *Shigella dysenteriae*. Shiga toxin (verotoxin) enters the circulation from the bowel and induces capillary endothelial damage, resulting in platelet activation with the formation of microthrombi. Platelet consumption causes **thrombocytopenia** whereas the microthrombi lead to erythrocyte damage (forming schistocytes) and the resultant **hemolytic anemia** (eg, pallor, weakness, tachycardia). Damage to glomerular endothelial cells also causes **acute kidney injury** (eg, oliguria/anuria, increased creatinine) in approximately 50% of cases.

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anemia (eg, pallor, weakness, tachycardia). Damage to glomerular endothelial cells also causes **acute kidney injury** (eg, oliguria/anuria, increased creatinine) in approximately 50% of cases.

The hemolytic anemia in HUS causes decreased hemoglobin and haptoglobin levels as well as increased serum lactate dehydrogenase and unconjugated bilirubin levels **(Choice A)**. The bleeding time may also be increased due to the reduced number of platelets. However, other coagulation studies are normal as there are no clotting factor deficiencies or disseminated intravascular coagulation associated with HUS **(Choices C and D)**.

(Choice E) Coombs test, or direct antiglobulin test, detects autoantibodies against red blood cells if they are present in the serum. The hemolytic anemia of HUS syndrome is mechanical rather than autoimmune; therefore, the Coombs test is negative.

(Choice F) Streptozyme testing detects antibodies against group A *Streptococcus* and can be used to retrospectively diagnose streptococcal infections (eg, when evaluating for post-streptococcal glomerulonephritis [PSGN]). However, children with PSGN have edema and hypertension, but no hemolytic anemia.

Educational objective:
Hemolytic uremic syndrome (HUS) manifests with acute kidney injury, microangiopathic hemolytic anemia,

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(Choices C and D).

(Choice E) Coombs test, or direct antiglobulin test, detects autoantibodies against red blood cells if they are present in the serum. The hemolytic anemia of HUS syndrome is mechanical rather than autoimmune; therefore, the Coombs test is negative.

(Choice F) Streptozyme testing detects antibodies against group A *Streptococcus* and can be used to retrospectively diagnose streptococcal infections (eg, when evaluating for post-streptococcal glomerulonephritis [PSGN]). However, children with PSGN have edema and hypertension, but no hemolytic anemia.

Educational objective:
Hemolytic uremic syndrome (HUS) manifests with acute kidney injury, microangiopathic hemolytic anemia, and thrombocytopenia. Characteristic laboratory abnormalities include decreased hemoglobin and platelet count and increased bleeding time, lactate dehydrogenase, bilirubin, blood urea nitrogen, and creatinine.

Pathophysiology	Hematology & Oncology	Hemolytic uremic syndrome
Subject	System	Topic

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A 52-year-old man comes to the office due to a progressively enlarging neck mass, fatigue, and weight loss over the past 2 months. Physical examination shows enlarged, firm, and nontender cervical lymph nodes. The patient also has enlarged tonsils, bilateral axillary lymphadenopathy, and splenomegaly. Excisional lymph node biopsy reveals diffuse sheets of atypical, large B cells that have replaced the normal tissue architecture. In situ hybridization of the tissue specimen is positive for Epstein-Barr virus. Which of the following risk factors is most strongly associated with development of this patient's condition?

- A. Advanced HIV infection (75%)
- B. Aspirin and nonsteroidal anti-inflammatory drug use (0%)
- C. Cigarette smoking (7%)
- D. Radiation exposure (9%)
- E. Socioeconomic status (6%)

Correct

75% Answered correctly

53 secs Time Spent

12/02/2020 Last Updated

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Explanation

This patient likely has **non-Hodgkin lymphoma** (NHL). Depending on the subtype, NHL may present with a rapidly progressive mass, lymphadenopathy, splenomegaly, and B symptoms (eg, night sweats, weight loss). Diagnosis is typically made with excisional lymph node biopsy, which usually demonstrates a loss of normal tissue architecture with expansion of abnormal lymphocytes (most often B cells, as in this patient with large, atypical B cells).

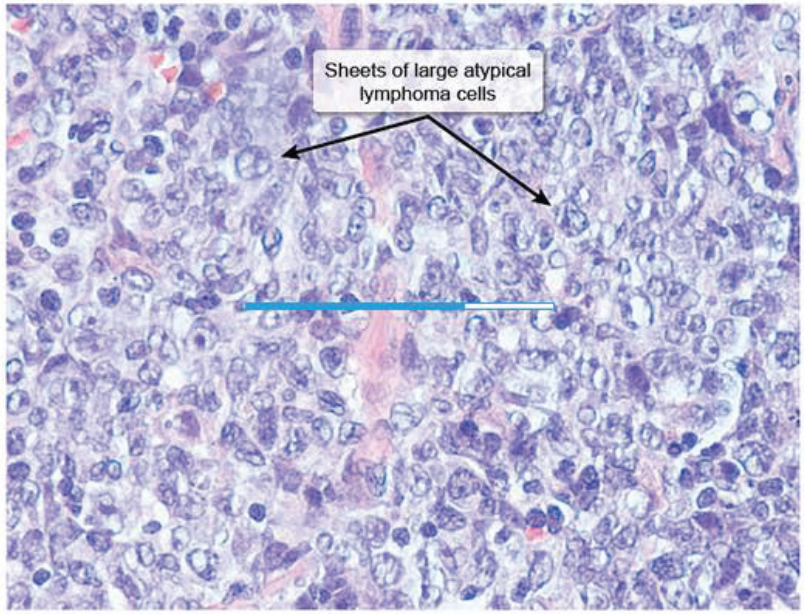
Lymphoma is frequently associated with **Epstein-Barr virus** (EBV), a ubiquitous herpesvirus that primarily infects B lymphocytes and causes persistent latent infections. Although viral reactivation is uncommon, the latent EBV genome still transcribes viral gene products that can result in **malignant transformation** of infected cells. EBV is particularly associated with nasopharyngeal carcinoma, Hodgkin lymphoma, and some forms of NHL (eg, Burkitt lymphoma).

Patients with **HIV** are at greatest risk for EBV-associated lymphomas (risk is up to 60-fold greater). This is likely due to HIV-related immune dysregulation, which decreases recognition of EBV-infected cells and promotes B-cell proliferation. Some types of NHL (eg, primary central nervous system lymphoma) are considered AIDS-defining conditions and can sometimes be the presenting manifestation of HIV infection.

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Diffuse large B-cell lymphoma*



*Most common type of non-Hodgkin lymphoma.

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(Choice B) Aspirin and nonsteroidal anti-inflammatory drugs may decrease the risk of colorectal cancer. Their use is not linked to an increased risk of NHL.

(Choice C) Cigarette smoking is a strong risk factor for the development of many types of cancer (eg, lung, bladder, pancreas) but is not closely linked with the development of NHL.

(Choice D) The link between radiation exposure and the development of NHL is controversial. However, most studies indicate that this is not a strong risk factor.

(Choice E) Although lower socioeconomic status may be associated with worse outcomes in patients with NHL, this marker has not been closely linked with the development of NHL.

Educational objective:
Patients with HIV have much higher rates of lymphoma than the general population. Many cases are due to underlying Epstein-Barr virus infection, which acts synergistically with HIV to promote uncontrolled B lymphocyte proliferation.

References

- EBV and HIV-related lymphoma.

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Hemoglobin C (HbC) disease is due to a single amino acid substitution (glutamic acid → lysine) at position 6 in the beta globin chain of the hemoglobin molecule. Hemoglobin S (HbS) is similar to HbC in that it is also formed by an amino acid substitution at position 6 in the beta globin chain. However, patients homozygous for HbC have mild chronic hemolytic anemia, whereas those homozygous for HbS generally have a more severe anemia complicated by vasoocclusive pain episodes. Which of the following properties best accounts for the differing clinical severity between the two conditions?

- A. HbS allows hydrophobic interaction among hemoglobin molecules (54%)
- B. HbS decreases beta globin interaction with 2,3-bisphosphoglycerate (6%)
- C. HbS impairs oxygen unloading from the heme moiety (8%)
- D. HbS prevents proper folding of the alpha helix in the beta globin chain (28%)
- E. HbS stabilizes the iron moiety in the ferric (Fe^{3+}) state (1%)

Correct

54% Answered correctly

01 min, 24 secs Time Spent

08/31/2020 Last Updated

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Globin chains in the hemoglobin tetramer are compactly folded due to nonpolar hydrophobic residues in the interior and charged polar residues on the surface. In **sickle cell disease**, the usual acidic (negatively charged) glutamic acid (glu) residue at the sixth position on the beta globin chain is replaced by a **nonpolar** (neutral charge) **valine** (val) residue, forming hemoglobin S (**HbS**). This single glu → val substitution leads to the formation of a **hydrophobic pocket** on the beta globin surface that interacts with a complementary nonpolar residue on another hemoglobin molecule. The hydrophobic interaction causes **polymerization** of HbS molecules and subsequent **erythrocyte sickling**, leading to membrane damage and permanent distortion of red blood cells. Red cell sickling is promoted by low oxygen levels, increased acidity, and dehydration.

In patients with hemoglobin C (**HbC**), glu is replaced by a basic **polar** (positively charged) **lysine** (lys) residue. Because lys is charged (although it has opposite polarity to glu), there is no hydrophobic interaction between hemoglobin molecules and no polymerization/sickling. However, the positive charge of lys causes HbC to have decreased mobility on electrophoresis.

(Choice B) HbS and HbC do not differ significantly from normal hemoglobin in affinity to 2,3-bisphosphoglycerate (2,3-BPG). In addition, weaker interaction with 2,3-BPG would lead to increased oxygen affinity (left shift of the oxygen-hemoglobin dissociation curve), which would help ameliorate sickling

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bisphosphoglycerate (2,3-BPG). In addition, weaker interaction with 2,3-BPG would lead to increased oxygen affinity (left shift of the oxygen-hemoglobin dissociation curve), which would help ameliorate sickling.

(Choice C) The ability of HbS to polymerize helps stabilize the deoxygenated form, causing a right shift of the oxygen-hemoglobin dissociation curve that facilitates oxygen unloading. In contrast, impaired oxygen unloading occurs with carboxyhemoglobin due to an allosteric change that increases the affinity of the remaining 3 oxygen-binding sites.

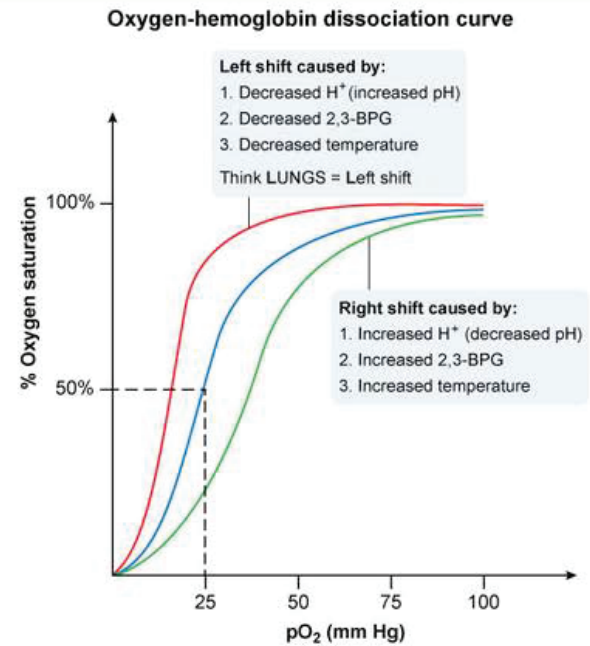
(Choice D) A glu → val substitution affects the 3-dimensional (tertiary) structure of hemoglobin, but it does not result in a significant change in the alpha helical (secondary) structure. Introducing proline into the primary structure could distort the alpha helix due to proline's rigid cyclic structure.

(Choice E) HbS and HbC mutations do not involve amino acids lining the heme pocket. Heme iron oxidation (ferrous [Fe^{2+}] → ferric [Fe^{3+}]) results in methemoglobin formation. Hemoglobin M disease is a congenital cause of methemoglobinemia due to a mutation in the heme-binding pocket.

Educational objective:
Hemoglobin S (HbS) contains valine in place of glutamic acid at the sixth amino acid position of the beta globin chain. This promotes hydrophobic interaction among Hb molecules and results in HbS

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globin chain. This promotes hydrophobic interaction among Hb molecules and results in HbS

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the oxygen-hemoglobin dissociation curve that facilitates oxygen unloading. In contrast, impaired oxygen unloading occurs with carboxyhemoglobin due to an allosteric change that increases the affinity of the remaining 3 oxygen-binding sites.

(Choice D) A glu → val substitution affects the 3-dimensional (tertiary) structure of hemoglobin, but it does not result in a significant change in the alpha helical (secondary) structure. Introducing proline into the primary structure could distort the alpha helix due to proline's rigid cyclic structure.

(Choice E) HbS and HbC mutations do not involve amino acids lining the heme pocket. Heme iron oxidation (ferrous [Fe^{2+}] → ferric [Fe^{3+}]) results in methemoglobin formation. Hemoglobin M disease is a congenital cause of methemoglobinemia due to a mutation in the heme-binding pocket.

Educational objective:
Hemoglobin S (HbS) contains valine in place of glutamic acid at the sixth amino acid position of the beta globin chain. This promotes hydrophobic interaction among Hb molecules and results in HbS polymerization and erythrocyte sickling.

Biochemistry	Hematology & Oncology	Sickle cell
Subject	System	Topic

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A 65-year-old man comes to the office due to a few weeks of progressive exertional dyspnea and fatigue. He has had no chest pain, fever, or cough. The patient has a history of mild aortic stenosis, gastroesophageal reflux disease, obesity, hypertension, and hypercholesterolemia. Temperature is 36.7 C (98 F), blood pressure is 130/78 mm Hg, pulse is 82/min, and respirations are 16/min. BMI is 28 kg/m^2. Pulse oximetry shows 96% on room air. Mucosal pallor is present, but there is no jaundice, lymphadenopathy, or jugular venous distension. Cardiopulmonary examination reveals a 2/6 systolic ejection murmur at the second right intercostal area. The abdomen is soft and nontender; there is no palpable hepatosplenomegaly. Peripheral pulses are normal. Laboratory results are as follows:

Complete blood count

Hemoglobin	7.8 g/dL
Platelets	98,000/mm^3
Leukocytes	3,800/mm^3

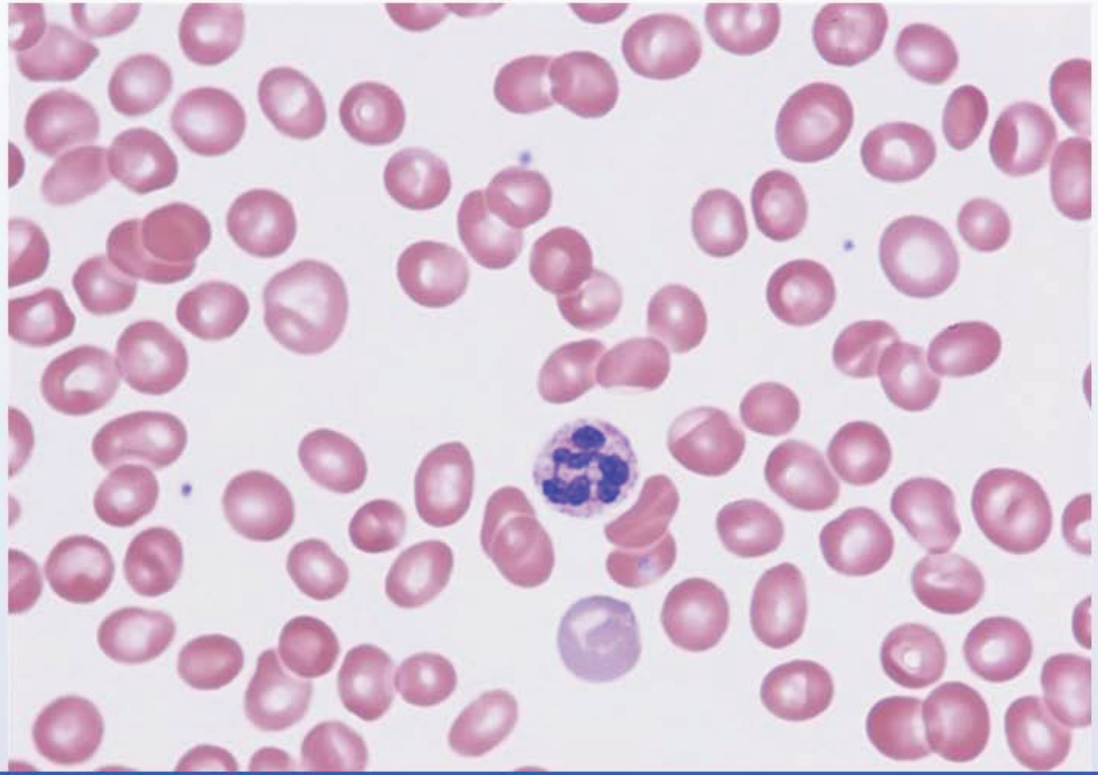
Peripheral blood smear is shown below:



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Peripheral blood smear is shown below:



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Which of the following is most likely responsible for this patient's current condition?

- A. Impaired DNA synthesis (70%)
- B. Impaired heme production (5%)
- C. Inadequate erythropoietin production (2%)
- D. Replacement of bone marrow with fat cells (9%)
- E. Replacement of bone marrow with fibrosis (7%)
- F. ~~Traumatic hemolysis~~ (4%)

Correct

70%
Answered correctly

04 mins, 16 secs
Time Spent

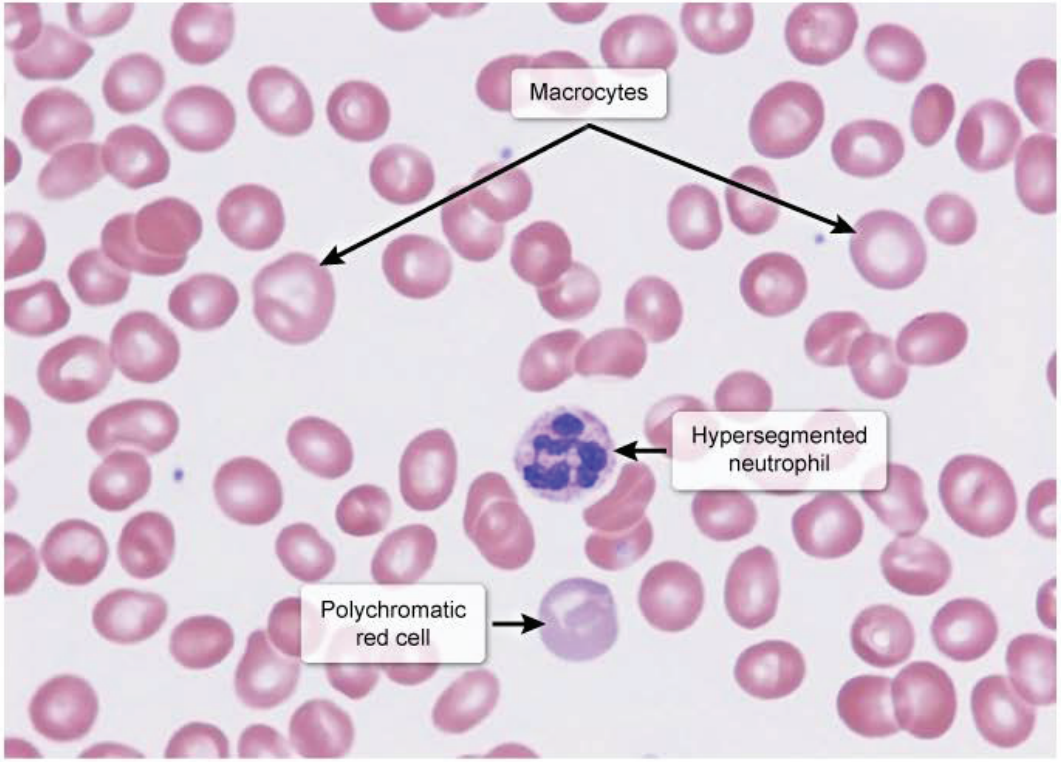
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Explanation

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Macrocytic anemia



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This patient with exertional dyspnea, fatigue, conjunctival pallor, and a systolic ejection murmur has symptomatic anemia. The presence peripheral blood smear findings of **macrocytosis** and a **hypersegmented neutrophil** indicate likely **megaloblastic anemia**. This condition sometimes arises in older individuals who take antacids for gastroesophageal reflux disease, as gastric acid is required for proper vitamin B_{12} absorption.

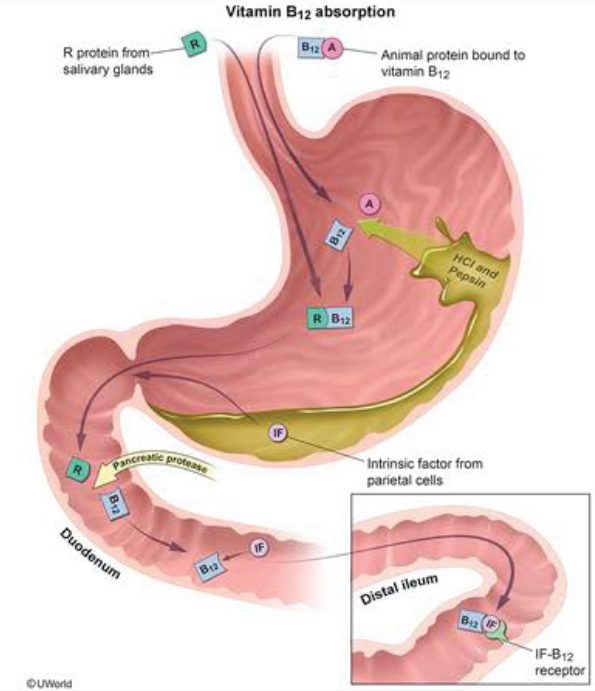
Vitamin B_{12} acts as a cofactor in the recycling of 5-methyl-tetrahydrofolate to tetrahydrofolate (reduced form of folate), which serves as a one-carbon donor in the synthesis of amino acids, purines, and thymidine monophosphate. Therefore, folate or **vitamin B_{12} deficiency** reduces available purines and thymidine, which **impairs DNA synthesis** and causes cell cycle arrest (in S-phase) or apoptotic cell death.

Hematopoietic cells are primarily affected due to their high replication rate. In these cells, nuclear division slows relative to cytoplasmic maturation (nuclear-cytoplasmic desynchrony), which results in **megaloblastic changes** (eg, macrocytosis, hypersegmented neutrophils); in addition, increased apoptosis causes **anemia** and often **mild thrombocytopenia/leukopenia**.

(Choice B) Iron deficiency anemia is associated with impaired production of heme; however, peripheral blood smear would show microcytosis (not macrocytosis), and no hypersegmented neutrophils would be

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slows relative to cytoplasmic maturation (nuclear-cytoplasmic desynchrony), which results in **megaloblastic changes** (eg, macrocytosis, hypersegmented neutrophils); in addition, increased apoptosis causes **anemia** and often **mild thrombocytopenia/leukopenia**.

(Choice B) Iron deficiency anemia is associated with impaired production of heme; however, peripheral blood smear would show microcytosis (not macrocytosis), and no hypersegmented neutrophils would be seen.

(Choice C) Chronic kidney disease can reduce production of erythropoietin in the peritubular cells of the kidney, which causes normocytic anemia due to reduced erythropoiesis. However, leukopenia and thrombocytopenia are not typically seen, and peripheral blood smear would not show megaloblastic changes.

(Choice D) Aplastic anemia is associated with destruction of hematopoietic stem cells and replacement of the bone marrow with fat cells. Although patients usually have pancytopenia, peripheral blood smear would not show macrocytosis or hypersegmented neutrophils.

(Choice E) Primary myelofibrosis is a chronic myeloproliferative disorder characterized by fibrosis of the bone marrow. Anemia is common but patients usually have dacrocytes (tear-drop cells) and nucleated red blood cells on peripheral blood smear, not macrocytosis and hypersegmented neutrophils.

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would not show macrocytosis or hypersegmented neutrophils.

(Choice E) Primary myelofibrosis is a chronic myeloproliferative disorder characterized by fibrosis of the bone marrow. Anemia is common but patients usually have dacrocytes (tear-drop cells) and nucleated red blood cells on peripheral blood smear, not macrocytosis and hypersegmented neutrophils.

(Choice F) Aortic stenosis can sometimes cause traumatic hemolysis due to red blood cell shearing. However, peripheral smear generally shows schistocytes, and thrombocytopenia/leukopenia would be unusual.

Educational objective:

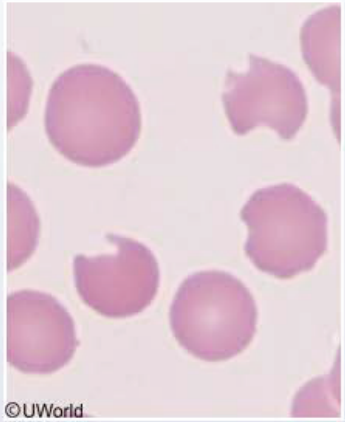
Vitamin B_{12} is an essential cofactor in the recycling of 5-methyl-tetrahydrofolate to tetrahydrofolate, which is required for amino acid, purine, and thymidine synthesis. Deficiency primarily affects hematopoietic cell maturation and is marked by increased nuclear-cytoplasmic ratio, leading to macrocytic red blood cells and hypersegmented neutrophils; increased apoptosis often also leads to anemia and mild thrombocytopenia/leukopenia.

Pathophysiology	Hematology & Oncology	Vitamin b12 deficiency
Subject	System	Topic

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A 24-year-old man is evaluated for episodic anemia, jaundice, and dark urine. These episodes typically occur after the use of certain drugs or following infection. Additional history reveals that he has a brother who experiences similar episodes. Peripheral blood smear reveals red blood cells with the findings shown below.



Deficiency of which of the following enzymes would most likely result in a condition similar to this patient's presentation?

A. Bisphosphoglycerate mutase (2%)

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Deficiency of which of the following enzymes would most likely result in a condition similar to this patient's presentation?

A. Bisphosphoglycerate mutase (2%)
B. Glutathione reductase (74%)
C. Hexokinase (2%)
D. Pyruvate kinase (14%)
E. Transketolase (5%)

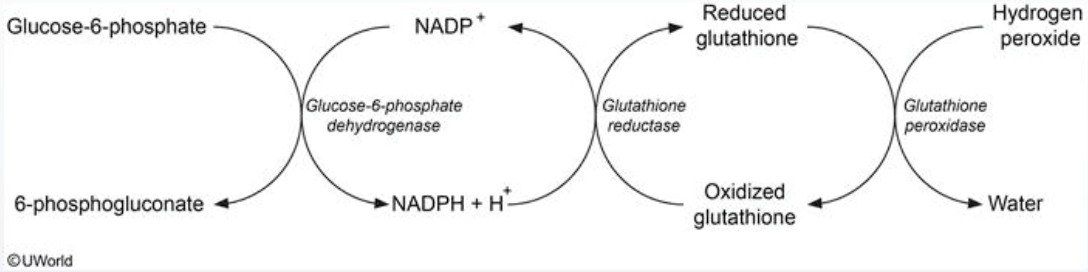
Correct

74% Answered correctly

02 mins, 04 secs Time Spent

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This patient likely has **glucose-6-phosphate dehydrogenase (G6PD) deficiency**, an X-linked recessive disorder causing hemolytic anemia and jaundice in response to oxidant stressors (eg, sulfonamide & antimalarial drugs, infection). Heinz bodies (oxidized hemoglobin conglomerates) precipitate in red blood cells and are removed by splenic macrophages, leaving behind characteristic bite cells.

G6PD is an enzyme of the **pentose phosphate pathway**. It generates the reducing agent **NADPH**, which is essential for detoxification of hydrogen peroxide produced by partial reduction of molecular oxygen in red blood cells. In the absence of NADPH, **reduced glutathione** (the molecule required for reduction of hydrogen peroxide to water) remains in an oxidized state, and red blood cells become susceptible to oxidative damage.

Glutathione reductase catalyzes the reduction of oxidized glutathione. Its absence leads to an inability to

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Glutathione reductase catalyzes the reduction of oxidized glutathione. Its absence leads to an inability to use NADPH to reduce glutathione, resulting in a clinical scenario **similar** to G6PD deficiency.

(Choice A) Bisphosphoglycerate mutase is an enzyme unique to red blood cells and placental cells. It catalyzes the production of 2,3-bisphosphoglycerate, a molecule that binds to hemoglobin and increases offloading of oxygen in the tissues.

(Choices C and D) Deficiency of the glycolytic enzymes hexokinase and pyruvate kinase leads to hemolytic anemia due to lack of ATP generation. However, these conditions would not present with bite cells and the hemolysis is not associated with exposure to oxidant stressors.

(Choice E) Transketolase, along with transaldolase, catalyzes the nonoxidative reactions of the pentose phosphate pathway, producing the ribose sugar necessary for nucleotide synthesis. The reducing equivalent NADPH is not generated in this portion of the pathway.

Educational objective:
Glucose 6-phosphate dehydrogenase deficiency causes hemolytic anemia and jaundice secondary to increased oxidative stress due to the lack of NADPH. Glutathione reductase deficiency has a similar clinical consequence as its absence results in an inability to utilize NADPH to reduce glutathione.

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A 28-year-old primigravid woman comes to the office for a routine prenatal checkup at 28 weeks gestation. The patient has no concerns and has had an uneventful pregnancy to date. Physical examination shows a uterine size concordant with ultrasound dates, and fetal cardiac activity is in the normal range. After reviewing the results of her laboratory evaluations, the physician administers an injection of anti-Rh(D) immunoglobulin. The administered antibodies most likely belong to which of the following immunoglobulin classes?

A. IgA (1%)
B. IgD (2%)
C. IgE (0%)
D. IgG (72%)
E. IgM (22%)

Incorrect
Correct answer
D

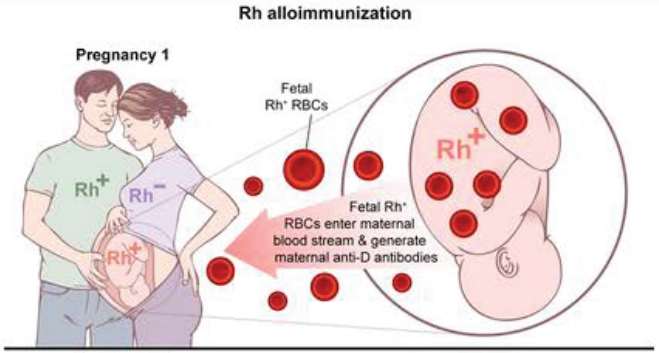
72%
Answered correctly

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RBCs = red blood cells.

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Rhesus (Rh) antigens are a group of nonglycosylated, transmembrane proteins found on the surface of red blood cells. The D antigen is the most immunogenic of the group and is present on the erythrocytes of Rh-positive individuals. When an Rh-negative mother becomes pregnant with an Rh-positive fetus, fetal red blood cells can enter the maternal circulation and elicit a maternal antibody response with the formation of memory B lymphocytes (**Rh alloimmunization**). After Rh alloimmunization occurs, subsequent pregnancies with Rh-positive fetuses will be at risk for **hemolytic disease of the newborn**.

To avoid maternal Rh alloimmunization, Rh-negative mothers must be prevented from mounting an immune response against the D antigen. **Anti-Rh(D) immunoglobulin** is a polyclonal antibody product consisting of **IgG anti-D** antibodies collected from pooled donor plasma. It is **administered to Rh-negative women** during gestation and in the immediate postpartum period. Once given, anti-Rh(D) antibodies bind to Rh-positive fetal erythrocytes that enter the maternal circulation, preventing their interaction with the maternal immune system by promoting sequestration and elimination in the mother's spleen (ie, the mononuclear phagocyte system).

Although IgG antibodies can cross the placenta, anti-Rh(D) IgG antibodies do not cause significant transplacental fetal hemolysis because the amount of antibody administered is negligible compared with

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transplacental fetal hemolysis because the amount of antibody administered is negligible compared with the amount produced in a typical immune hemolytic reaction.

(Choice A) IgA is primarily a mucosal antibody. Patients with IgA deficiency can have an anaphylactic reaction during the administration of intravenous immunoglobulin.

(Choice B) IgD is present in very low concentrations in the blood and is typically coexpressed with IgM as a B-cell membrane receptor.

(Choice C) IgE plays a significant role in allergic responses and in the immune response to parasitic infections.

(Choice E) Multivalent IgM antibodies are generally more effective than IgG antibodies at promoting agglutination of foreign antigens and activating complement, which would result in lysis of fetal erythrocytes in the maternal circulation. However, macrophages do not have receptors for IgM; therefore, anti-D IgM does not provide the same immunoprophylactic effect (eg, sequestration and clearance of Rh-positive erythrocytes) as anti-D IgG.

Educational objective:
Anti-Rh immunoglobulin consists of anti-D IgG antibodies that bind to Rh-positive fetal erythrocytes, promoting clearance by maternal reticuloendothelial macrophages and preventing maternal Rh

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(Choice B) IgD is present in very low concentrations in the blood and is typically coexpressed with IgM as a B-cell membrane receptor.

(Choice C) IgE plays a significant role in allergic responses and in the immune response to parasitic infections.

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Educational objective:

Anti-Rh immunoglobulin consists of anti-D IgG antibodies that bind to Rh-positive fetal erythrocytes, promoting clearance by maternal reticuloendothelial macrophages and preventing maternal Rh sensitization. It is routinely administered to Rh-negative women during gestation and immediately postpartum.

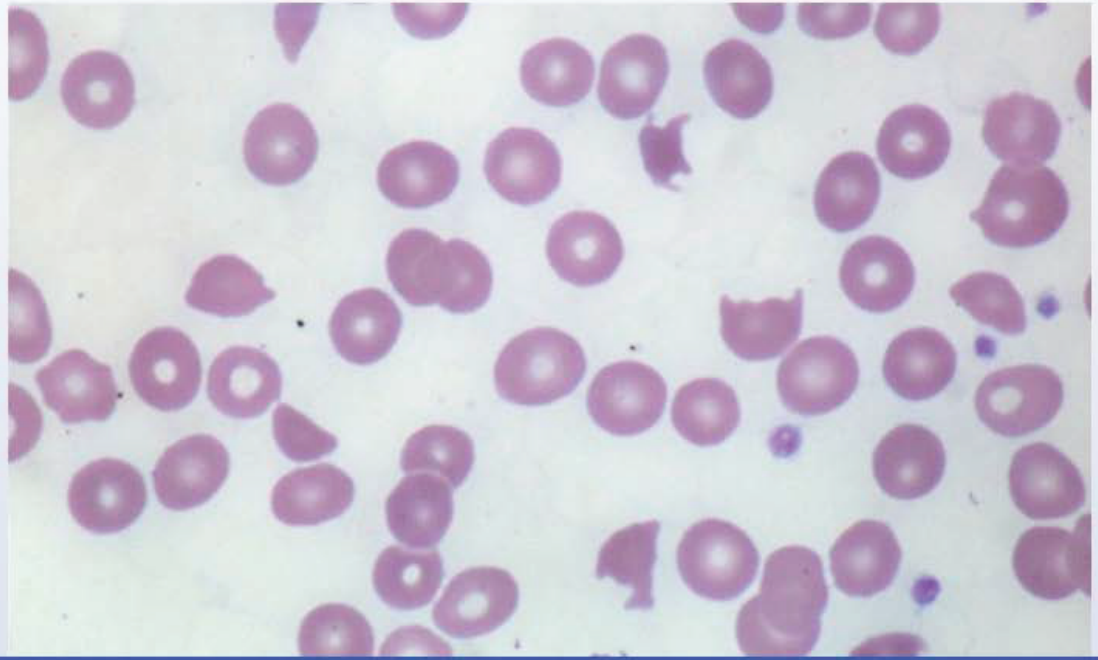
References

- Mechanisms of anti-D action in the prevention of hemolytic disease of the fetus and newborn.

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A 56-year-old man is evaluated for increased fatigability. His past medical history is significant for diabetes mellitus, osteoarthritis, and severe aortic stenosis that required aortic valve replacement. His peripheral blood smear is shown on the slide below.



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Which of the following laboratory findings is most likely to be seen in this patient?

A. Increased total serum iron level (7%)

B. Decreased serum haptoglobin level (82%)

C. Increased mean corpuscular volume (4%)

D. Decreased reticulocyte count (4%)

E. Decreased serum albumin level (1%)

Correct

82%
Answered correctly

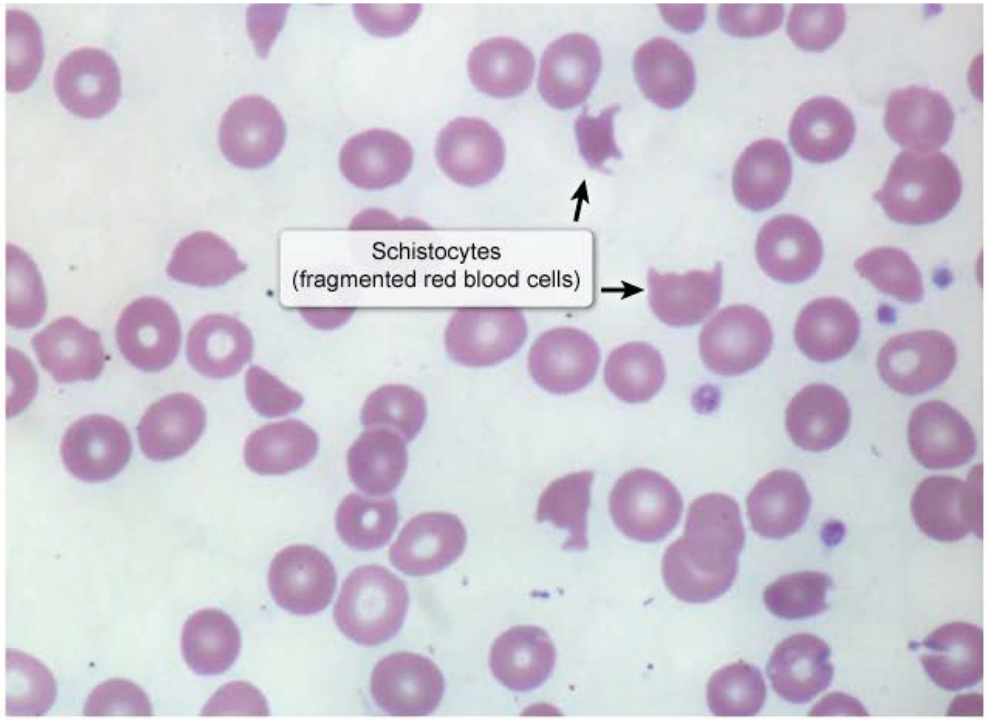
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Last Updated

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Schistocytes



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The fragmented erythrocytes shown on the slide above are called **schistocytes** or helmet cells. They are formed by **mechanical trauma** to erythrocytes as they circulate through the vasculature. This patient's schistocytes are most likely due to erythrocyte damage caused by his **aortic valve prosthesis**. Artificial (mechanical) valves are more traumatic for RBCs than porcine prostheses and frequently cause hemolysis. Schistocytes can also be formed from narrowing of the microvascular spaces, as seen in disseminated intravascular coagulation, hemolytic-uremic syndrome, and thrombotic thrombocytopenic purpura.

Hemolytic anemia due to intravascular erythrocyte destruction results in laboratory findings similar to those in other types of hemolytic anemias, including an increase in serum indirect bilirubin. Intravascular erythrocyte damage also results in free hemoglobin in serum (hemoglobinemia) and urine (hemoglobinuria) as well as increased serum lactate dehydrogenase (LDH). Haptoglobin is a serum protein that binds to free hemoglobin and promotes its uptake by the reticuloendothelial system. **Haptoglobin levels decrease** when significant quantities of hemoglobin are released into the circulation, as occurs with intravascular hemolysis.

(Choice A) Increased serum iron occurs in hemochromatosis most classically, but increased serum iron

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hemolysis.

(Choice A) Increased serum iron occurs in hemochromatosis most classically, but increased serum iron can also be iatrogenic. Hemochromatosis does not cause anemia, but it is associated with cirrhosis and increased incidence of hepatocellular cancer. Hemolysis does not usually have a significant effect on serum iron because the iron released from lysed RBCs remains bound to hemoglobin.

(Choice C) Increased mean corpuscular volume (MCV) occurs in megaloblastic anemia (eg, folate/vitamin B12 deficiency) due to the presence of enlarged ovoid erythrocytes. Increased MCV may also occur with other forms of anemia due to a reactive increase in reticulocytes (large, immature RBCs); however, anemia caused by mechanical erythrocyte trauma usually results in decreased MCV due to the presence of small RBC fragments (schistocytes).

(Choice D) A decreased reticulocyte count in the presence of anemia is characteristic of aplastic anemia. In hemolytic anemias, the reticulocyte count is increased to compensate for the increased destruction of RBCs.

(Choice E) A decreased serum albumin level is associated with cirrhosis (decreased production), nephrotic syndrome (urinary loss), and protein-wasting enteropathy (bowel loss).

Educational objective:

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caused by mechanical erythrocyte trauma usually results in decreased MCV due to the presence of small RBC fragments (schistocytes).

(Choice D) A decreased reticulocyte count in the presence of anemia is characteristic of aplastic anemia. In hemolytic anemias, the reticulocyte count is increased to compensate for the increased destruction of RBCs.

(Choice E) A decreased serum albumin level is associated with cirrhosis (decreased production), nephrotic syndrome (urinary loss), and protein-wasting enteropathy (bowel loss).

Educational objective:
Schistocytes (helmet cells) are fragmented erythrocytes. They occur secondary to mechanical trauma from microangiopathic hemolytic anemias or prosthetic cardiac valves (macroangiopathic). Intravascular hemolytic anemias are characterized by decreased serum haptoglobin levels as well as increased LDH and bilirubin.

Pathology	Hematology & Oncology	Hemolytic anemia
Subject	System	Topic

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A 14-year-old boy with chronic anemia is being evaluated after experiencing several episodes of chest, back, and extremity pain. Peripheral blood smear shows sickle-shaped red cells. Genetic testing reveals that the patient is homozygous for a point mutation in the beta-globin gene, resulting in a glutamic acid to valine substitution at position 6. Sequencing of the beta-globin gene would most likely reveal which of the following changes? (The genetic code is shown in the figure below.)

First position (5' end)	Second position				Third position (3' end)
	U/T	C	A	G	
U/T	Phe Phe Leu	Ser Ser Ser	Tyr Tyr Stop	Cys Cys Stop	U/T C A

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Exhibit Display

First position (5' end)	Second position				Third position (3' end)
	U/T	C	A	G	
U/T	Phe Phe Leu Leu	Ser Ser Ser Ser	Tyr Tyr Stop Stop	Cys Cys Stop Trp	U/T C A G
C	Leu Leu Leu Leu	Pro Pro Pro Pro	His His Gln Gln	Arg Arg Arg Arg	U/T C A G
A	Ile Ile Ile Met	Thr Thr Thr Thr	Asn Asn Lys Lys	Ser Ser Arg Arg	U/T C A G
G	Val Val Val Val	Ala Ala Ala Ala	Asp Asp Glu Glu	Gly Gly Gly Gly	U/T C A G

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	Met	Thr	Lys	Arg	**G**
G	Val Val Val Val	Ala Ala Ala Ala	Asp Asp Glu Glu	Gly Gly Gly Gly	**U/T** **C** **A** **G**

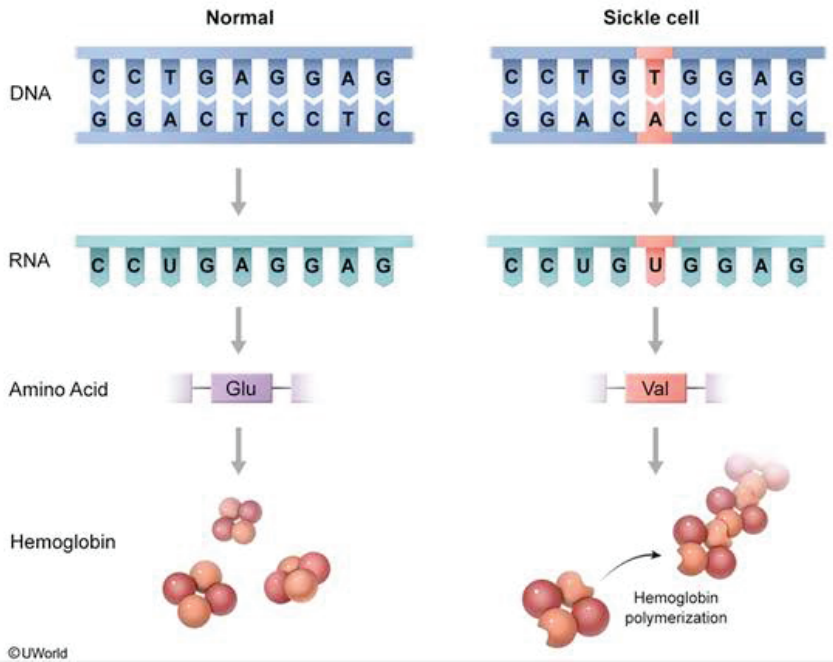
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- A. CAA → GTT (4%)
- B. CAT → CTT (1%)
- C. TTA → CTA (1%)
- D. GAA → GUA (25%)
- ✓ E. GAG → GTG (61%)
- F. GTA → GAA (5%)

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Sickle cell disease



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This patient has **sickle cell disease** (SCD), an autosomal recessive hematologic disorder resulting in hemoglobin molecules that polymerize during times of hypoxic stress. SCD results from a DNA point mutation in the coding region of the hemoglobin beta-globin chain. This single nucleotide substitution is a missense mutation that causes a **glutamic acid to valine substitution at position 6** during protein translation. The genetic code figure shows that 2 distinct nucleotide combinations code for glutamic acid, GAG and GAA. In addition, only 2 possible single nucleotide substitutions could occur in DNA that result in glutamic acid being replaced by valine, GAA → GTA and **GAG → GTG**.

(Choices A, B, and F) Examples of missense mutations include glutamine (CAA) substitution by valine (GTT), histidine (CAT) substitution by leucine (CTT), and valine (GTA) substitution by glutamic acid (GAA). However, they are unrelated to SCD.

(Choice C) This substitution results in a silent mutation as both TTA and CTA code for leucine.

(Choice D) A codon change from GAA to GUA also results in glutamic acid being replaced by valine. However, the pyrimidine base uracil occurs only in RNA (not DNA), so it would only be present in the mRNA transcript that codes for the beta-globin protein and not in the beta-globin gene itself.

Educational objective:

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polymerization

Exhibit Display

Types of DNA mutations	
Silent	Base substitution codes for same amino acid
Missense	Base substitution codes for different amino acid
Conservative	Base substitution codes for different amino acid with similar chemical structure
Nonsense	Base substitution introduces premature stop codon
Nonstop	Base substitution within stop codon results in continued translation
Splice site	Mutation at splice site alters intron removal from pre-mRNA
Frameshift	Deletion/insertion of bases causes downstream misreading

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Educational objective:

(Choices A, B, and F) Examples of missense mutations include glutamine (CAA) substitution by valine (GTT), histidine (CAT) substitution by leucine (CTT), and valine (GTA) substitution by glutamic acid (GAA). However, they are unrelated to SCD.

(Choice C) This substitution results in a silent mutation as both TTA and CTA code for leucine.

(Choice D) A codon change from GAA to GUA also results in glutamic acid being replaced by valine. However, the pyrimidine base uracil occurs only in RNA (not DNA), so it would only be present in the mRNA transcript that codes for the beta-globin protein and not in the beta-globin gene itself.

Educational objective:
Sickle cell disease is the result of a missense mutation that causes valine to replace glutamic acid at position 6 in the hemoglobin beta-globin chain. RNA contains the pyrimidine base uracil, whereas DNA contains the base thymidine.

References

- Sickle cell pathophysiology

Genetics	Hematology & Oncology	Sickle cell
Subject	System	Topic

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A 55-year-old man comes to the office due to several months of progressive fatigue. He does not have chest pain or shortness of breath. Medical history is significant for hypertension and obesity. BMI is 45 kg/m^2. Examination shows mild mucosal pallor. Laboratory results are as follows:

Complete blood count	
Hemoglobin	8.6 g/dL
Mean corpuscular volume	84 µm^3
Reticulocytes	0.2%
Platelets	200,000/mm^3
Leukocytes	7,500/mm^3
Serum chemistry	
Blood urea nitrogen	14 mg/dL
Creatinine	0.8 mg/dL

Which of the following is the most likely cause of this patient's anemia?

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Reticulocytes	0.2%
Platelets	200,000/mm^3
Leukocytes	7,500/mm^3
Serum chemistry	
Blood urea nitrogen	14 mg/dL
Creatinine	0.8 mg/dL

Which of the following is the most likely cause of this patient's anemia?

- A. Anemia of chronic inflammation (52%)
- B. Extravascular hemolysis (8%)
- C. Microangiopathic hemolytic anemia (6%)
- D. Occult blood loss (29%)
- E. Vitamin B_{12} deficiency (2%)

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Anemia of chronic disease	
Pathogenesis	• ↑ inflammatory cytokines (eg, hepcidin) • Inhibition of ferroportin on enterocytes and macrophages • ↓ iron absorption and ↑ iron sequestration • Reduced circulating iron → impaired erythropoiesis
Common Etiologies	• Malignancy • Chronic infection • Rheumatic disease • Obesity • Diabetes mellitus • Congestive heart failure
Laboratory findings	• Normocytic/slightly microcytic anemia • ↓ serum iron, iron-binding capacity, reticulocyte count • ↑ bone marrow iron • Lower than expected erythropoietin for degree of anemia

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Laboratory findings	• ↓ serum iron, iron-binding capacity, reticulocyte count • ↑ bone marrow iron • Lower than expected erythropoietin for degree of anemia
Treatment	• Treat underlying condition causing inflammation

This patient with morbid obesity has normocytic anemia with a low reticulocyte count, raising strong suspicion for **anemia of chronic disease** (ACD). Because ACD is triggered by **long-standing elevations in serum inflammatory cytokines**, it is classically associated with underlying rheumatologic disease, persistent infection, or malignancy. However, ACD is also commonly caused by less obvious sources of inflammation such as type 2 diabetes mellitus, congestive heart failure, severe traumatic injury, and **morbid obesity**.

The major inflammatory cytokine that drives ACD is **hepcidin**, a small peptide released from the liver in response to inflammation or bacterial lipopolysaccharide. Hepcidin binds to and **inhibits iron channels** (ferroportin) on the surface of enterocytes and reticuloendothelial macrophages, leading to decreased iron absorption in the gut and decreased iron release by the reticuloendothelial system (which supplies ~95% of daily iron for erythropoiesis). Because heme synthesis is impaired without sufficient iron, patients with ACD typically develop a **normocytic** (or slightly microcytic) **anemia** with a **minimal reticulocyte response**.

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typically develop a **normocytic** (or slightly microcytic) **anemia** with a **minimal reticulocyte response**.

(Choice B) Extravascular hemolysis typically occurs due to the formation of IgG autoantibodies against the erythrocyte membrane, which results in erythrocyte destruction by splenic macrophages. Patients generally develop an acute normocytic anemia with a strong (not suppressed) reticulocyte response.

(Choice C) Microangiopathic hemolytic anemia is associated with shearing of red blood cells in the microvasculature due to the formation of fibrin-rich platelet clots. Patients typically have normocytic anemia, significant reticulocytosis, and severe thrombocytopenia (~10,000/mm^3).

(Choice D) Iron deficiency anemia (IDA) from an occult gastrointestinal bleed is common in older individuals. IDA is also associated with a low reticulocyte count. Although IDA can cause mild normocytic anemia early in the disease course, by the time individuals develop profound anemia (eg, hemoglobin of 8.6 mg/dL), they almost always have severe microcytosis (eg, MCV < 70). This patient's severe anemia is accompanied by a normal MCV, making iron deficiency anemia highly unlikely.

(Choice E) Vitamin B_{12} deficiency is associated with macrocytic (not normocytic) anemia due to impaired maturation of erythrocytes.

Educational objective:
Anemia of chronic disease (ACD) occurs in patients with rheumatologic diseases, chronic infection,

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anemia, significant reticulocytosis, and severe thrombocytopenia (~10,000/mm^3).

(Choice D) Iron deficiency anemia (IDA) from an occult gastrointestinal bleed is common in older individuals. IDA is also associated with a low reticulocyte count. Although IDA can cause mild normocytic anemia early in the disease course, by the time individuals develop profound anemia (eg, hemoglobin of 8.6 mg/dL), they almost always have severe microcytosis (eg, MCV < 70). This patient's severe anemia is accompanied by a normal MCV, making iron deficiency anemia highly unlikely.

(Choice E) Vitamin B_{12} deficiency is associated with macrocytic (not normocytic) anemia due to impaired maturation of erythrocytes.

Educational objective:
Anemia of chronic disease (ACD) occurs in patients with rheumatologic diseases, chronic infection, malignancy, congestive heart failure, and morbid obesity due to chronic elevation of inflammatory cytokines. The primary mediator is hepcidin, a peptide released from the liver that inhibits iron channels on enterocytes and reticuloendothelial macrophages. This reduces iron availability for erythropoiesis, which leads to normocytic (or slightly microcytic) anemia with a poor reticulocyte response.

Pathophysiology	Hematology & Oncology	Anemia of inflammation
Subject	System	Topic

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A 23-year-old Italian American man comes to the clinic for a follow-up visit. He was found to have mild anemia during a routine checkup 3 weeks ago and was started on iron supplementation. He has been taking the supplements as prescribed. The patient has otherwise been well. He feels that his energy levels are normal, and he has run several half-marathons in the last 2 years. The patient's initial hemoglobin level was 12.3 g/dL. Laboratory results obtained during today's visit are as follows:

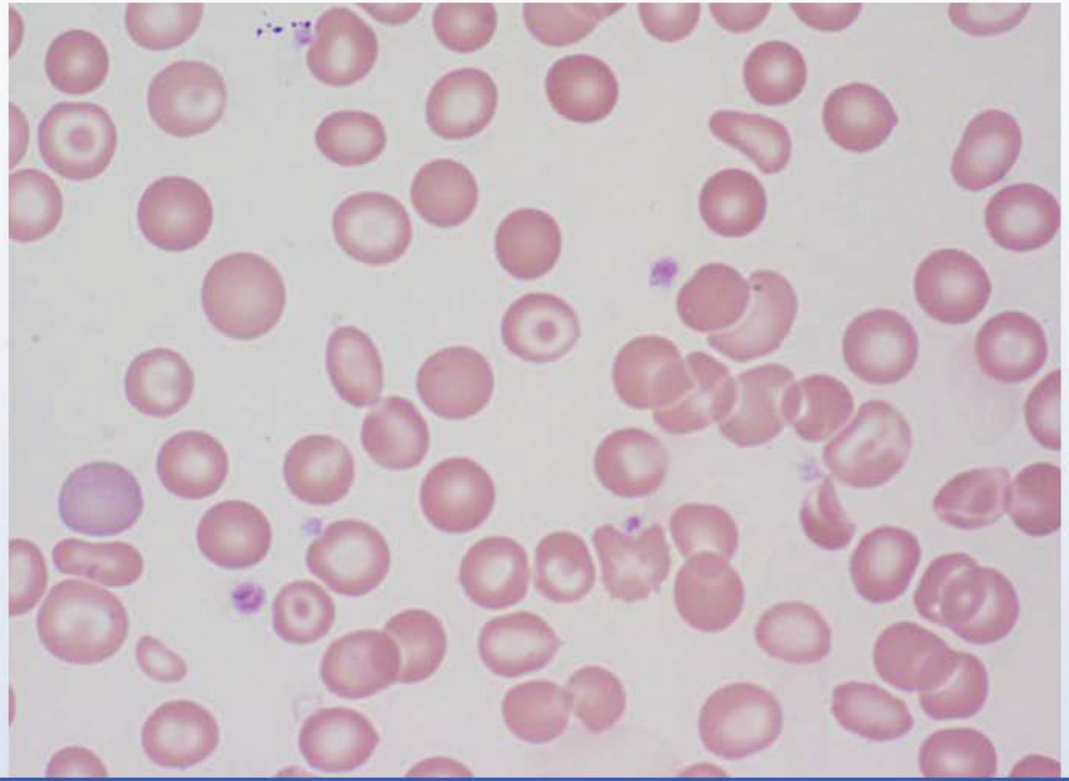
Hemoglobin	12.2 g/dL
Erythrocyte count	5.8 million/mm^3
Mean corpuscular volume	70 µm^3
Leukocytes	6,500/mm^3
Platelets	180,000/mm^3
Hemoglobin A2	6% (normal 1%-3%)

The patient's blood smear is shown in the image below:

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The patient's blood smear is shown in the image below.



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Which of the following processes is the initial step in the pathogenesis of this patient's disorder?

- A. Cell membrane stability (13%)
- B. DNA replication (7%)
- C. Heme synthesis (25%)
- D. Intracellular oxidant detoxification (3%)
- ✓ E. mRNA formation (29%)
- F. Protein folding (18%)
- G. Protein solubility (2%)

Correct

29%

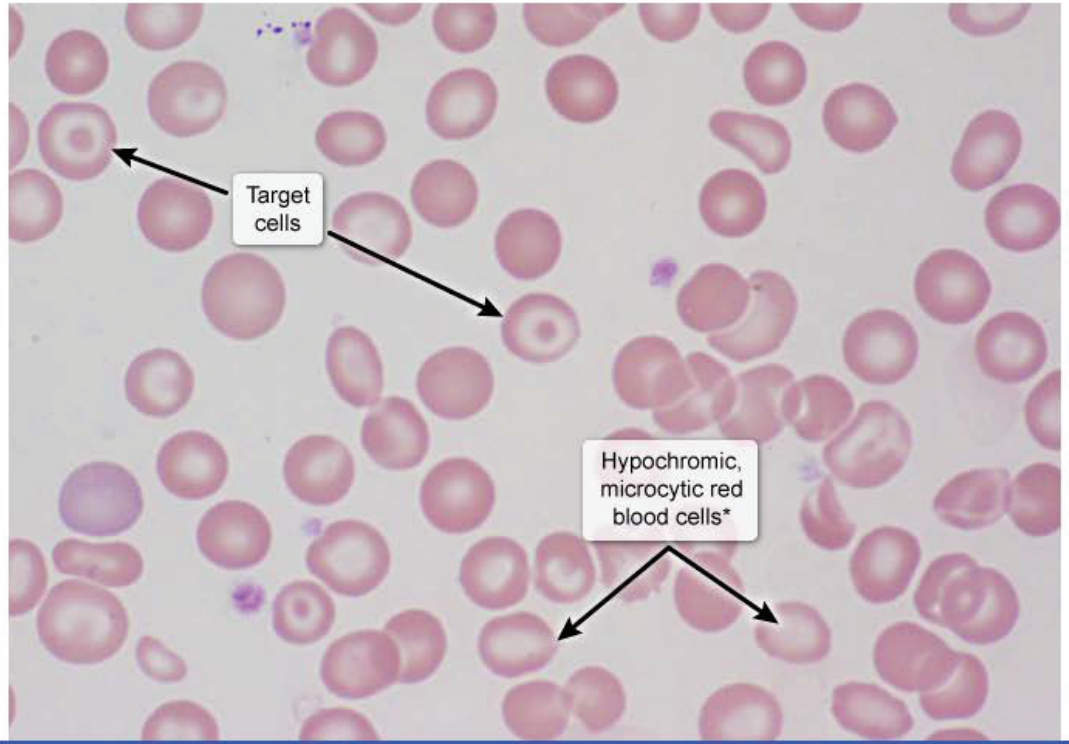
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Beta thalassemia



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*Pale, small red blood cells

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This patient has a **microcytic** (mean corpuscular volume [MCV] <75 μm^3) anemia and increased **hemoglobin A2** (α2δ2) concentration. His peripheral blood smear shows hypochromia and poikilocytes, including spherocytes and target cells (arrows). This constellation of findings in an asymptomatic adult of Mediterranean heritage suggests **beta-thalassemia minor**. Beta-thalassemia is the most common thalassemia in patients of Mediterranean descent; alpha-thalassemia is more common in individuals from Southeast Asia. The microcytic anemia is often incorrectly attributed to iron deficiency, but iron supplements do not benefit these patients as they are not iron deficient.

Normal adult hemoglobin (hemoglobin A) contains 2 alpha chains and 2 beta chains (α2β2) in combination with heme. Beta-thalassemia affects beta-chain production and can be caused by a variety of DNA mutations affecting the **transcription, processing**, and **translation** of beta-globin **mRNA**. Most commonly, these mutations cause aberrant precursor mRNA splicing or premature chain termination during mRNA translation. In some cases, point mutations prevent RNA polymerase from binding to the promoter region. The resulting beta-globin deficiency occurs in the setting of normal heme and alpha-chain synthesis, leading to increased formation of hemoglobin A2 and (in some patients) **hemoglobin F** (α2γ2).

(Choices A and G) Decreased beta-chain synthesis in beta-thalassemia results in the formation of

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insoluble alpha-chain tetramers that precipitate within red blood cells. This can affect the membrane cytoskeleton and reduce membrane stability. However, the initial pathogenic abnormality in beta-thalassemia is a deficiency in beta-chain synthesis.

(Choice B) In patients with beta-thalassemia, the DNA replicates normally despite the mutations in the beta-globin gene. It is not until the DNA is transcribed into mRNA that hemoglobin production becomes abnormal. Anemias due to DNA synthesis defects include the megaloblastic anemias (vitamin B_{12} or folic acid deficiency), which are characterized by an elevated MCV (>100 μm^3).

(Choice C) Heme is an iron-containing porphyrin that is incorporated into globin proteins to form hemoglobin. Globin synthesis, not heme synthesis, is abnormal in thalassemia syndromes. Porphyrias are disorders of heme synthesis.

(Choice D) Impaired intracellular oxidant detoxification occurs with glucose-6-phosphate dehydrogenase deficiency, a cause of hemolytic anemia.

(Choice F) An example of a protein folding defect is that caused by the Z mutation in the gene coding for alpha-1 antitrypsin.

Educational objective:

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(Choice D) Impaired intracellular oxidant detoxification occurs with glucose-6-phosphate dehydrogenase deficiency, a cause of hemolytic anemia.

(Choice F) An example of a protein folding defect is that caused by the Z mutation in the gene coding for alpha-1 antitrypsin.

Educational objective:

Beta-thalassemia is caused by mutations that result in defective transcription, processing, and translation of beta-globin mRNA. This leads to deficiency of the beta-globin chains required for normal hemoglobin synthesis.

References

- Control of human beta-globin mRNA stability and its impact on beta-thalassemia phenotype.
- Update on fetal hemoglobin gene regulation in hemoglobinopathies.

Pathophysiology	Hematology & Oncology	Thalassemia
Subject	System	Topic

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A 64-year-old man comes to the office due to a lump in his neck. He has a long history of using chewing tobacco. On examination, there is an ulcerative lesion in the left floor of mouth. There is also a firm, palpable, nontender left submandibular mass. Biopsy of the submandibular mass is shown in the exhibit. Which of the following is the most likely route of spread from the floor of mouth to the submandibular mass?

A. ~~Direct invasion through the floor of mouth~~ (10%)

B. ~~Field cancerization of the oral cavity mucosa~~ (14%)

✓ C. Lymphatic drainage to the submandibular lymph nodes (69%)

D. ~~Perineural spread through the lingual nerve~~ (1%)

E. ~~Sublingual vein to the submandibular gland~~ (4%)

Correct

69%
Answered correctly

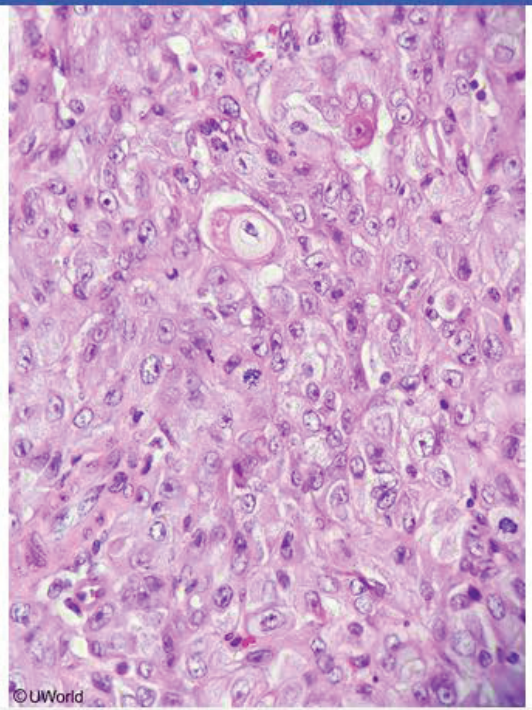
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Cancer routes of spread		
Type	**Definition**	**Examples**
Direct invasion	Extension into neighboring tissues	• Most cancers
Lymphatics	Embolic drainage or invasion into lymphatic channels allows spread to regional lymph nodes	• Most carcinomas
Hematogenous	Embolic spread through the vasculature (usually veins)	• Sarcomas • Renal cell carcinoma • Hepatocellular carcinoma
Transcoelomic	Spread throughout a body cavity	• Ovarian tumor → surface of the liver
Perineural	Spread along nerves or nerve sheaths	• Pancreatic ductal adenocarcinoma • Prostate cancer

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This patient with an ulcerative lesion in the floor of mouth and ipsilateral lymphadenopathy in the submandibular area has a biopsy that shows malignant cells with **atypical mitotic figures and keratin pearls**, findings which are consistent with head and neck mucosal squamous cell carcinoma (HNSCC).

Most **carcinomas**, including head and neck squamous cell carcinoma, first **spread** from the primary site of the tumor to **regional lymph nodes** via the **lymphatics**. In this patient with a floor of mouth squamous cell carcinoma, the spread is to the upper anterior cervical lymph nodes, manifesting as submandibular lymphadenopathy.

Assessment of regional lymph node status is important for tumor staging based on the **TNM staging system**, which evaluates the size and characteristics of the **T**umor, regional lymph **N**ode involvement, and distant **M**etastases. The presence of metastases is indicative of advanced cancer and often confers a poor prognosis.

(Choice A) Direct invasion through the floor of mouth can occur in head and neck squamous cell carcinoma and result in extension to the submandibular space. However, it is likely to present as a large, fungating mass with local destruction (eg, bony invasion).

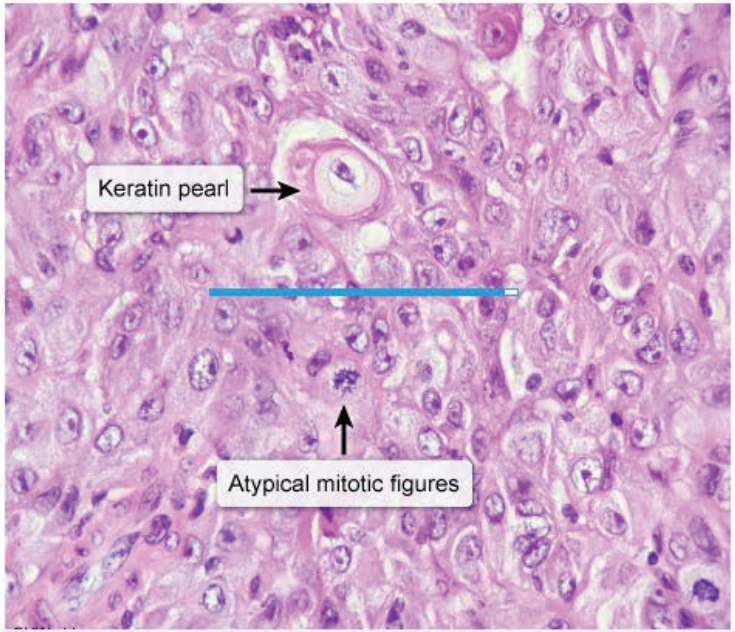
(Choice B) Field cancerization refers to widespread, premalignant damage to cells in a large area. It is

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Exhibit Display

Metastatic SCC in a lymph node



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fungating mass with local destruction (eg, bony invasion).

(Choice B) Field cancerization refers to widespread, premalignant damage to cells in a large area. It is thought to be responsible for the high rate of synchronous tumors in patients with head and neck squamous cell carcinomas.

(Choice D) Perineural invasion occurs in many cancers, including head and neck cancer, and conveys a poor prognosis. It may contribute to some symptoms of cancer, including numbness or pain, but is not responsible for disease in the lymph nodes of this patient.

(Choice E) Hematogenous spread of cancer typically follows venous drainage routes and is common in sarcomas and a few carcinomas (eg, renal cell carcinoma, hepatocellular carcinoma); however, it is not typical in head and neck squamous cell carcinoma.

Educational objective:

Head and neck squamous cell carcinomas typically spread first to the anterior cervical lymph nodes via the lymphatics. The involvement of anterior cervical lymph nodes affects the staging of the disease.

References

- The molecular biology of head and neck cancer.

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A 57-year-old male presents to your office complaining of fatigue and low energy. He also notes experiencing intermittent back pain that responds to ibuprofen. He has no significant past medical history. His family history is significant for his father dying of a heart attack at age 60. Fecal occult blood testing is negative. Laboratory studies reveal:

Hematocrit	36%
MCV	86 fl
WBC	7,000/mm^3
Platelets	170,000/mm^3
Sodium	136 mEq/L
Potassium	4.5 mEq/L
AST	34 U/L
ALT	18 U/L
Bilirubin	0.8 mg/dL

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Potassium	4.5 mEq/L
AST	34 U/L
ALT	18 U/L
Bilirubin	0.8 mg/dL
Creatinine	2.0 mg/dL

Plasma protein electrophoresis reveals a high peak corresponding to gamma-globulins. The most likely diagnosis is:

A. Iron deficiency (3%)
B. Cobalamin deficiency (1%)
C. Chronic lymphocytic leukemia (5%)
D. Aplastic anemia (3%)
E. Plasma cell neoplasm (81%)
F. Hodgkin lymphoma (2%)

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In multiple myeloma, neoplastic B-lymphocytes mature into plasma cells that synthesize abnormal (typically large) amounts of monoclonal immunoglobulin or immunoglobulin fragments (e.g. light chains). Clinical manifestations of multiple myeloma include impaired hematopoiesis leading to a normochromic, normocytic anemia and weakness; lytic bone lesions classically affecting the vertebral column and causing back pain and pathologic fractures; and hypercalcemia and AL amyloidosis, which contribute to renal dysfunction. Severe amyloidosis can also cause cardiac and cutaneous findings.

The classic laboratory abnormalities in multiple myeloma include erythrocyte rouleaux formation on peripheral blood smear and Bence-Jones proteins in the urine. Serum protein electrophoresis (SPEP) is a more specific laboratory test used to determine if excessive monoclonal immunoglobulins are present in the serum. An "M peak" on SPEP indicates the presence of such an immunoglobulin. (An M peak may also be found in Waldenstrom macroglobulinemia and some lymphomas.)

(Choices A and B) Iron deficiency can cause weakness due to a hypochromic, microcytic anemia and vitamin B12 (cobalamin) deficiency can cause weakness due to a macrocytic anemia. Vitamin B12 deficiency can also cause neurologic signs.

(Choice C) CLL is a lymphocytic malignancy that may cause a normochromic, normocytic anemia, but immunoglobulin production is classically depressed, not increased, in CLL.

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deficiency can also cause neurologic signs.

(Choice C) CLL is a lymphocytic malignancy that may cause a normochromic, normocytic anemia, but immunoglobulin production is classically depressed, not increased, in CLL.

(Choice D) Aplastic anemia would cause a uniform depression of all hematologic cell lines, including leukocytes and platelets.

(Choice F) Hodgkin lymphoma is a B-cell malignancy characterized by the presence of Reed-Sternberg cells on lymph node histology. There may be anemia of chronic disease in patients with this condition, but a monoclonal gammopathy would not be expected.

(Choice G) Patients with hypothyroidism may be anemic due to associated iron deficiency or pernicious anemia. However, monoclonal gammopathy would not be expected.

Educational Objective:
The finding of a high peak in the gamma-globulin region on serum protein electrophoresis (SPEP) usually represents an M protein consisting of an overproduced monoclonal immunoglobulin. Multiple myeloma causes an M protein peak on SPEP as well as anemia (weakness), lytic bone lesions (back pain, pathologic fractures), and renal insufficiency (related to amyloid deposition and hypercalcemia).

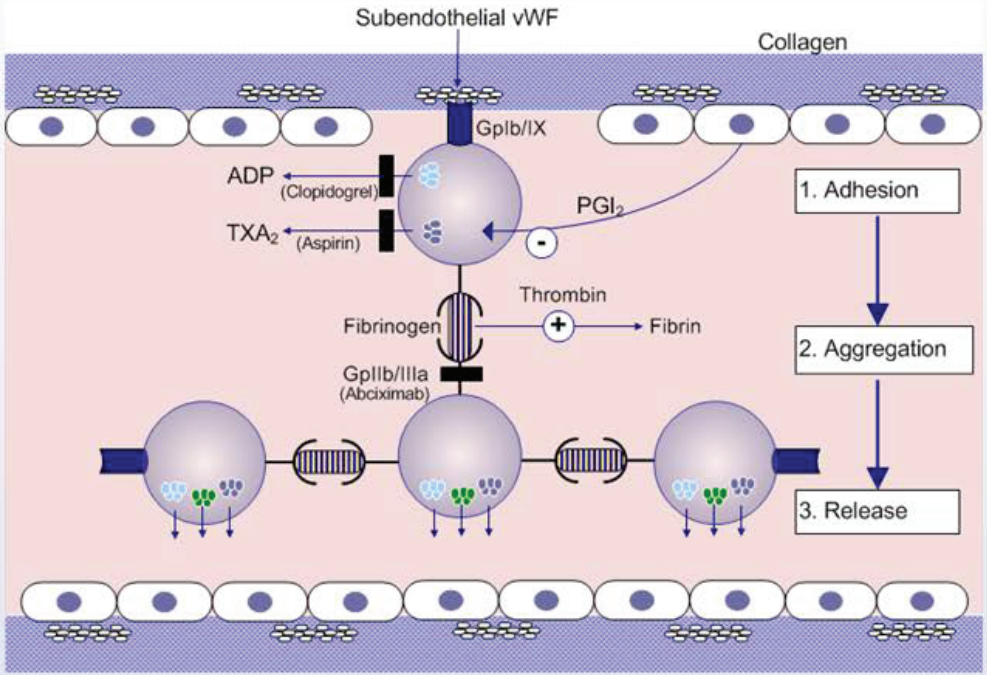
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A 23-year-old man is evaluated for excessive bruising since childhood. He says some of his family members "bleed easily" and sometimes require blood transfusions. Temperature is 36.7 C (98.1 F). Physical examination is unremarkable. Complete blood cell count is unremarkable. Platelet aggregometry is abnormal. Genetic testing identifies a defect in a platelet surface glycoprotein receptor that normally binds fibrinogen to support platelet aggregation. The abnormal glycoprotein receptor found in this patient is most likely targeted by which of the following medications?

- A. Abciximab (66%) ✓
- B. Argatroban (4%)
- C. Aspirin (2%)
- D. Clopidogrel (21%) ✗
- E. Dabigatran (2%)
- F. Heparin (2%)
- G. Warfarin (0%)

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This patient likely has Glanzmann thrombasthenia, an autosomal recessive disorder that is caused by a deficient or defective **glycoprotein (GP) IIb/IIIa** on platelet surfaces and that typically presents in childhood with mucocutaneous bleeding. Peripheral smear shows no platelet clumping (an important clue for

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This patient likely has Glanzmann thrombasthenia, an autosomal recessive disorder that is caused by a deficient or defective **glycoprotein (GP) IIb/IIIa** on platelet surfaces and that typically presents in childhood with mucocutaneous bleeding. Peripheral smear shows no platelet clumping (an important clue for diagnosis).

Platelets are responsible for formation of platelet plugs that stop bleeding from injured vessels (**primary hemostasis**). Vessel wall injury exposes the subendothelial collagen and matrix. Platelet attachment to exposed collagen is strengthened by GP Ib binding to von Willebrand factor on the vessel wall. The resulting platelet activation leads to the following:

- Release of mediators (eg, ADP, thromboxane A2 [TXA2]) into circulation, which in turn activates other platelets
- Conformational structural change of **GP IIb/IIIa** on platelet surfaces; this allows thousands of copies of GP IIb/IIIa to bind **fibrinogen**, thereby forming a **platelet plug**.

Abciximab, a **GP IIb/IIIa receptor antagonist**, inhibits binding of this receptor to fibrinogen. Abciximab and other GP IIb/IIIa inhibitors are useful for treatment of unstable angina and acute coronary syndrome, particularly in patients undergoing percutaneous coronary intervention.

(Choices B, E, F, and G) Argatroban (used in heparin-induced thrombocytopenia) and dabigatran (used in

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and other GP IIb/IIIa inhibitors are useful for treatment of unstable angina and acute coronary syndrome, particularly in patients undergoing percutaneous coronary intervention.

(Choices B, E, F, and G) Argatroban (used in heparin-induced thrombocytopenia) and dabigatran (used in atrial fibrillation or venous thromboembolism) are direct thrombin inhibitors. Heparin potentiates antithrombin III activity, leading to inactivation of thrombin and factor Xa; warfarin prevents K-mediated carboxylation of several coagulation factors. All these medications have anticoagulant effects.

(Choices C and D) Aspirin, a cyclooxygenase (COX)-1 and 2 inhibitor, inhibits TXA2 (via platelet COX acetylation), thereby preventing platelet aggregation. Clopidogrel inhibits platelet aggregation by blocking P2Y12 on platelet ADP receptors.

Educational objective:
Abciximab is a blocker of glycoprotein (GP) IIb/IIIa receptor, which normally promotes platelet binding to fibrinogen. GP IIb/IIIa is either deficient or defective in patients with Glanzmann thrombasthenia.

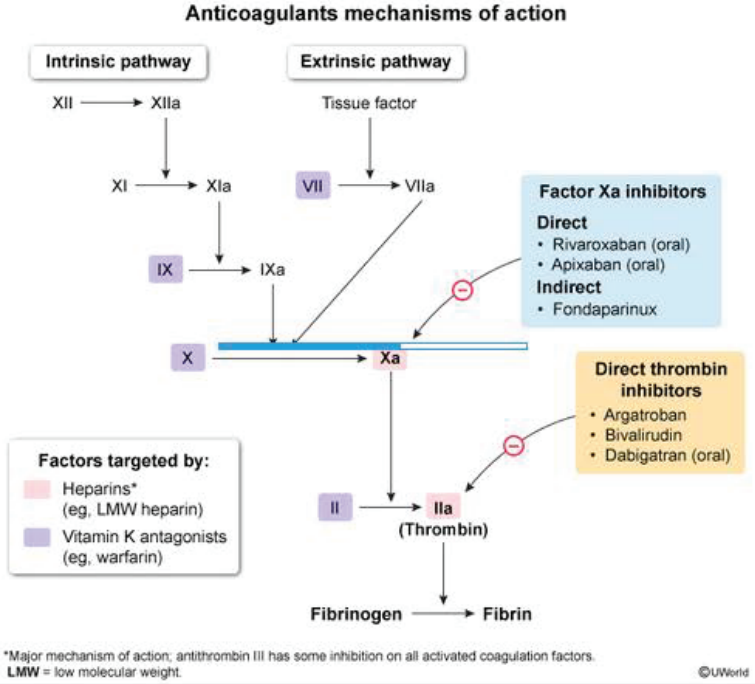
Pharmacology	Hematology & Oncology	Glanzmann thrombasthenia
Subject	System	Topic

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and other GP IIb/IIIa inhibitors are useful for treatment of unstable angina and acute coronary syndrome

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A 52-year-old woman comes to the office due to 2 weeks of constant back pain. She has also had several months of nonproductive cough, anorexia, and unintentional weight loss. The patient has a 40-pack-year smoking history. Physical examination shows diffuse muscle wasting, left lung crackles, and vertebral tenderness. Imaging reveals a left lung mass and lytic lesions in the vertebrae. Further evaluation confirms metastatic non-small cell lung cancer. Treatment with a cisplatin-based chemotherapy is begun, and the patient is also started on a neurokinin-1 receptor antagonist. The latter medication is most likely to improve which of the following in this patient?

- A. Chemotherapy-induced nausea (84%)
- B. Malignancy-related anorexia (4%)
- C. Metastases-related hypercalcemia (2%)
- D. Opioid-induced constipation (1%)
- E. Tumor lysis-induced renal failure (6%)

84% 01 min, 12 secs 08/23/2020

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Common antiemetic drugs			
Drug class	**Examples**	**Clinical uses**	**Major side effects**
Antimuscarinics (anticholinergics)	• Scopolamine	• Vestibular nausea • Motion sickness	• Anticholinergic effects (eg, dry mouth, sedation)
Antihistamines	• Meclizine		
Dopamine receptor antagonists (DRAs)	• Prochlorperazine • Metoclopramide • Chlorpromazine	• Migraine headache (DRAs) • Acute or chronic nausea/vomiting • Acute chemotherapy-induced emesis	• Extrapyramidal reactions
Serotonin (5-HT_3) receptor antagonists	• Ondansetron • Granisetron		• QT prolongation
Neurokinin-1 (NK1) receptor antagonists	• Aprepitant • Fosaprepitant	• Delayed chemotherapy-induced emesis	• Neutropenia

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		induced emesis	

Chemotherapy-induced nausea and vomiting (CINV) is a common side effect of cancer treatment. It is caused by both peripheral and central mechanisms, as follows:

- **Acute-phase CINV** (<24 hours after chemotherapy) is mediated primarily by the release of **serotonin** from intestinal enterochromaffin cells that have been damaged by chemotherapy. Serotonin stimulates vagal afferent fibers (5-HT3 receptors) in the bowel wall, which project to the brainstem and stimulate the vomiting reflex. Therefore, **serotonin receptor antagonists** (eg, ondansetron) can be used for treatment.
- **Delayed-phase CINV** (1-5 days after chemotherapy) is mediated primarily by increased levels of **substance P** in the brainstem due to chemotherapy-associated emetic stimuli in the cerebrospinal fluid and bloodstream. Substance P binds to and activates the **neurokinin-1** (NK1) **receptor** in areas of the brainstem that mediate vomiting (eg, nucleus tractus solitarius, area postrema). Therefore, **NK1 receptor antagonists** (eg, aprepitant, fosaprepitant) are often used for treatment.

Most patients who undergo chemotherapy associated with a high risk of vomiting (eg, cisplatin) receive a combination of serotonin receptor antagonists and NK1 receptor antagonists (often with other antiemetics) to prevent both types of CINV.

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to prevent both types of CINV.

(Choice B) Malignancy-related anorexia is the loss of muscle and fat caused by elevated levels of circulating inflammatory cytokines. Progesterone analogs (eg, megestrol acetate) are the first-line treatment; corticosteroids and cannabinoids are also frequently used.

(Choice C) Malignancy-related hypercalcemia is typically treated with bisphosphonates (eg, zoledronic acid), which reduce osteoclast-mediated bone resorption.

(Choice D) Opioid-induced constipation occurs due to opioid-mediated effects on the bowel wall, which reduce peristalsis. Methylnaltrexone, an opioid antagonist that has limited ability to cross the blood-brain barrier (it does not trigger withdrawal), can be used as treatment.

(Choice E) Patients who have highly aggressive lymphomas and leukemias are at risk for tumor lysis syndrome (TLS) with chemotherapy. Its primary manifestation is renal damage from elevated uric acid levels (catabolism of nucleic acids released from tumor cells increases uric acid). Rasburicase, a drug that breaks down uric acid, is used to prevent TLS in high-risk patients.

Educational objective:
Chemotherapy-induced nausea and vomiting is mediated by peripheral and central mechanisms. It can be treated with serotonin receptor antagonists (eg, ondansetron) to prevent serotonin stimulation of afferent

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(Choice C) Malignancy-related hypercalcemia is typically treated with bisphosphonates (eg, zoledronic acid), which reduce osteoclast-mediated bone resorption.

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Educational objective:
Chemotherapy-induced nausea and vomiting is mediated by peripheral and central mechanisms. It can be treated with serotonin receptor antagonists (eg, ondansetron) to prevent serotonin stimulation of afferent vagal fibers in the bowel wall (peripheral cause) and neurokinin-1 receptor antagonists (eg, aprepitant) to prevent the effects of substance P in the brainstem (central cause).

Pharmacology Hematology & Oncology Chemotherapy induced nausea and vomiting

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A 9-year-old boy with a history of sickle cell disease is brought to the office due to fatigue. The patient takes penicillin, hydroxyurea, and folic acid daily. Temperature is 37.1 C (98.8 F), blood pressure is 102/68 mm Hg, pulse is 130/min, and respirations are 20/min. Examination shows conjunctival pallor. The oropharynx is clear and the neck is supple. The lungs are clear to auscultation bilaterally, and the abdomen is soft with normal bowel sounds; there is no organomegaly. Skin examination is unremarkable. Laboratory results are as follows:

Hemoglobin	5.8 g/dL
Mean corpuscular volume	116 μm^3
Reticulocytes	0.5%
Platelets	90,000/mm^3
Leukocytes	3,000/mm^3

Which of the following is the most likely cause of this patient's findings?

A. Antibiotic-associated autoimmune hemolysis (5%)

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Mean corpuscular volume	116 μm³
Reticulocytes	0.5%
Platelets	90,000/mm³
Leukocytes	3,000/mm³

Which of the following is the most likely cause of this patient's findings?

A. Antibiotic-associated autoimmune hemolysis (5%)
B. Decreased methyl group donors involved in DNA synthesis (22%)
C. Loss of complement inhibition in hematopoietic stem cells (4%)
✓ D. Medication-induced inhibition of a nucleic acid synthesis enzyme (55%)
E. Sequestration of cells in the reticuloendothelial system (12%)

Correct

55% Answered correctly
03 mins, 20 secs Time Spent
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Causes of pancytopenia	
Bone marrow aplasia	• Aplastic anemia • Infection (eg, parvovirus, HIV, viral hepatitis) • Nutritional deficiency (eg, vitamin B_{12}/folate) • Medications (eg, hydroxyurea)
Bone marrow infiltration	• Cancer (eg, hematologic, metastatic) • Myelofibrosis • Infection (eg, tuberculosis, fungal infection)
Mature blood cell destruction	• Intravascular (eg, DIC, TTP) • Extravascular (eg, hypersplenism)

DIC = disseminated intravascular coagulation; **TTP** = thrombotic thrombocytopenic purpura.

This patient with sickle cell disease (SCD) has **pancytopenia**, a decrease in all 3 blood cell lineages. Pancytopenia is caused by hematopoietic stem cell dysfunction, bone marrow infiltration, or peripheral destruction of mature blood cells. Important clues in this case include:

Low reticulocyte count: Patients with severe anemia usually have increased reticulocytes due to

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DIC = disseminated intravascular coagulation; **TTP** = thrombotic thrombocytopenic purpura.

This patient with sickle cell disease (SCD) has **pancytopenia**, a decrease in all 3 blood cell lineages. Pancytopenia is caused by hematopoietic stem cell dysfunction, bone marrow infiltration, or peripheral destruction of mature blood cells. Important clues in this case include:

- **Low reticulocyte count:** Patients with severe anemia usually have increased reticulocytes due to enhanced bone marrow erythropoiesis. The presence of pancytopenia with an **inappropriately low** reticulocyte count usually indicates the **bone marrow is impaired** and is unable to adequately generate new cells despite strong growth signals (eg, increased erythropoietin).
- **Macrocytosis:** Although macrocytosis can be seen in a wide range of pathologies, the presence of pancytopenia plus macrocytosis usually indicates a vitamin deficiency (eg, vitamin B_{12}, folate) or a medication (eg, hydroxyurea) is **impairing DNA synthesis** in hematopoietic cells.

Hydroxyurea inhibits **ribonucleoside reductase**, an enzyme that generates deoxyribonucleoside triphosphates for **DNA synthesis/repair**. A lack of deoxyribonucleoside triphosphates slows erythrocyte nuclear development, leading to decreased cellular division with an overall increase in erythrocyte size. High doses of hydroxyurea also impair nuclear development in precursors of leukocytes and thrombocytes, leading to pancytopenia.

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leading to pancytopenia.

Hydroxyurea is the major disease-modifying medication in SCD; it reduces production of the mutated beta globulin gene and increases production of the fetal hemoglobin gene, which increases fetal hemoglobin (HbF). Because HbF functions normally, erythrocytes with increased HbF are less likely to sickle in the microvasculature.

(Choice A) Autoimmune hemolytic anemia is associated with high (not low) reticulocytes due to increased erythropoiesis. Because reticulocytes are larger (MCV 125-135 μm^3) than mature erythrocytes, reticulocytosis can cause macrocytosis; however, leukopenia and thrombocytopenia would not be seen.

(Choice B) Folate is a methyl group donor for the synthesis of purines and pyrimidines. Folate deficiency impairs DNA synthesis, which can lead to pancytopenia and macrocytosis. However, this patient is taking folic acid, making deficiency unlikely.

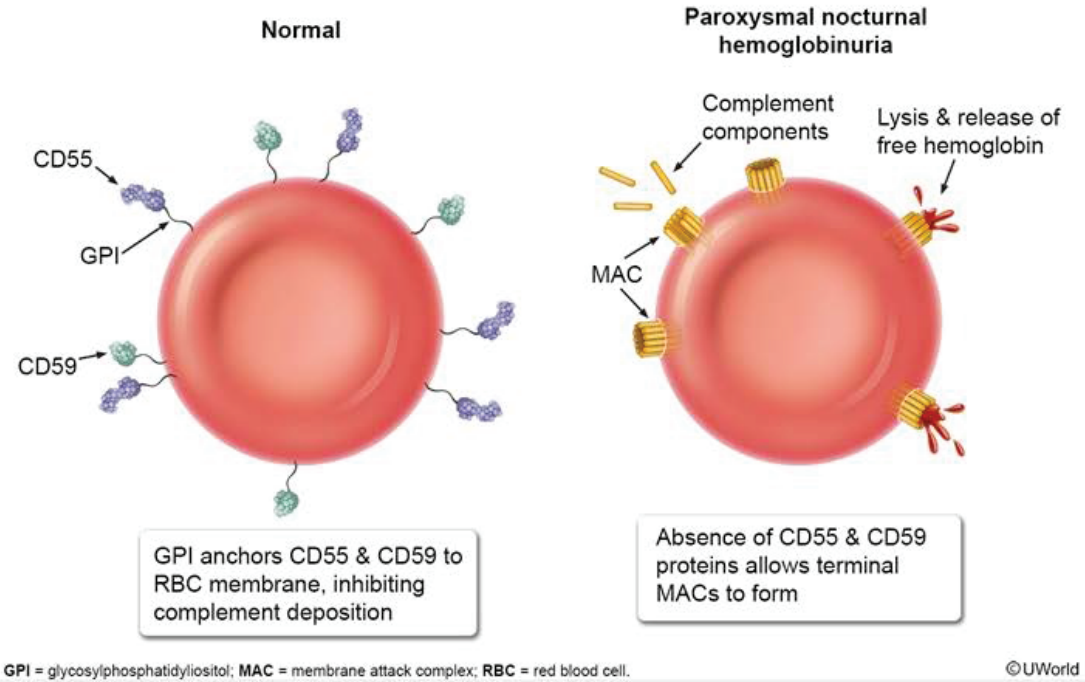
(Choice C) Paroxysmal nocturnal hemoglobinuria is an acquired disorder of hematopoietic stem/progenitor cells marked by lack of complement inhibitor on the erythrocyte surface. Hemolytic anemia is the primary manifestation; reticulocytosis is common, and pancytopenia rarely occurs.

(Choice E) SCD can cause hypersplenism due to splenic congestion with damaged erythrocytes. Although this can occasionally cause pancytopenia, patients with hypersplenism usually have

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leading to pancytopenia.

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(Choice E) SCD can cause hypersplenism due to splenic congestion with damaged erythrocytes. Although this can occasionally cause pancytopenia, patients with hypersplenism usually have splenomegaly and normocytic (not macrocytic) anemia.

Educational objective:
Hydroxyurea increases fetal hemoglobin production, which reduces erythrocyte sickling in patients with sickle cell disease. It also inhibits ribonucleoside reductase, which decreases deoxynucleoside triphosphates available for DNA synthesis; this leads to macrocytosis and, with high doses, pancytopenia.

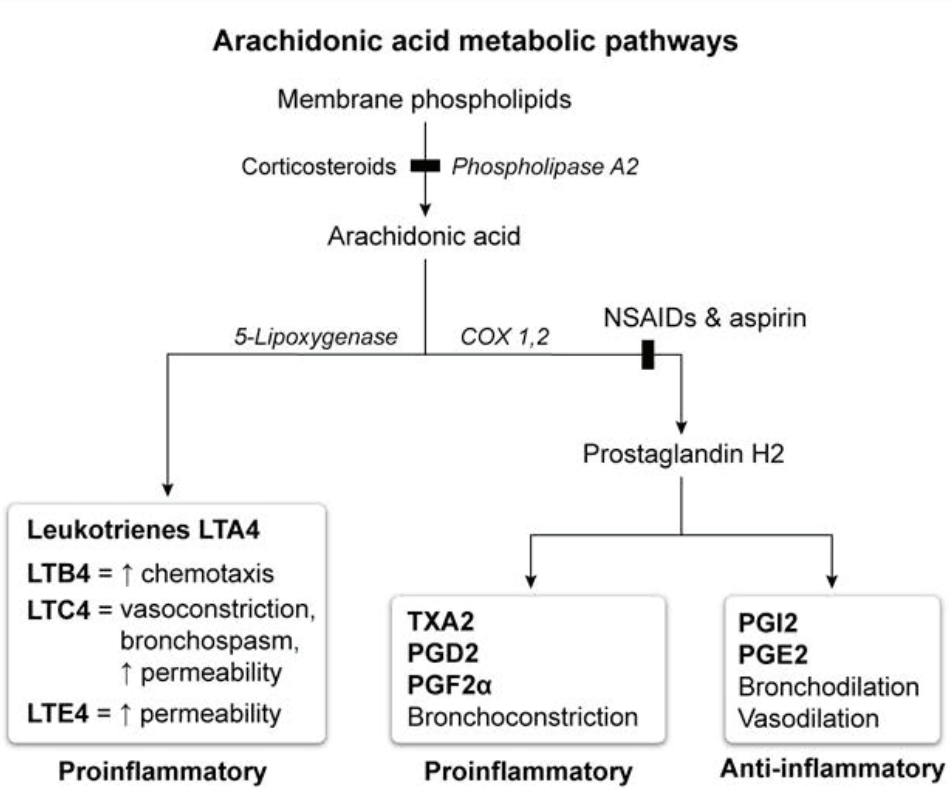
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A 52-year-old man recovering from an acute myocardial infarction develops new-onset chest pain that is relieved by leaning forward. The pain is exacerbated with deep inspiration. The patient was admitted with acute inferior myocardial infarction 2 days ago and did not undergo revascularization due to his late presentation. Since admission, he has had no chest pain until this morning. On physical examination, a friction rub is present at the left sternal border. The patient is treated with a medication that inhibits COX-1 and COX-2 enzymes via irreversible acetylation, resulting in significant relief of his symptoms. Which of the following agents was most likely used in this patient?

- A. Acetaminophen (1%)
- ✓ B. Aspirin (91%)
- C. Budesonide (0%)
- D. Celecoxib (2%)
- E. Colchicine (0%)
- F. Diclofenac (0%)
- G. Ibuprofen (1%)

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This patient's presentation of recent (within 1-3 days) myocardial infarction, pleuritic chest pain improved by leaning forward, and a friction rub on cardiac examination likely indicates peri-infarction pericarditis. Although most patients with peri-infarction pericarditis improve with supportive measures, those with sufficient or persistent symptoms are typically treated with aspirin in combination with colchicine.

Aspirin (acetylsalicylic acid) is a nonsteroidal anti-inflammatory drug (NSAID) that **irreversibly inhibits** cyclooxygenase-1 and -2 (**COX-1 and -2**) enzymes via **acetylation**, preventing conversion of arachidonic acid to prostaglandins, prostacyclin, and thromboxane. COX-1 acetylation inhibits generation of thromboxane A_2 in platelets (antithrombotic effect). COX-2 acetylation blocks prostaglandin production in inflammatory cells (eg, activated lymphocytes, neutrophils), resulting in anti-inflammatory, antipyretic, and analgesic effects.

(Choice A) Acetaminophen is an analgesic and antipyretic agent that reversibly inhibits COX enzymes (primarily in the central nervous system). It lacks anti-inflammatory properties due to its weak inhibition of COX in peripheral tissues.

(Choice C) Budesonide is a glucocorticoid agent with potent anti-inflammatory activity. Corticosteroids reduce COX-2 expression and decrease synthesis of arachidonic acid via phospholipase A_2 inhibition.

(Choice D) Celecoxib is a selective COX-2 inhibitor that provides anti-inflammatory benefits without

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(Choice D) Celecoxib is a selective COX-2 inhibitor that provides anti-inflammatory benefits without interfering with the physiological functions of COX-1. In contrast to the non-selective NSAIDs, selective COX-2 inhibitors have no significant effect on platelet function and are associated with a lower incidence of gastrointestinal bleeding. However, selective COX-2 inhibition is associated with an increased incidence of thrombosis.

(Choice E) Colchicine exerts its anti-inflammatory effects by inhibiting polymerization of beta-tubulin into microtubules, preventing migration and activation of neutrophils.

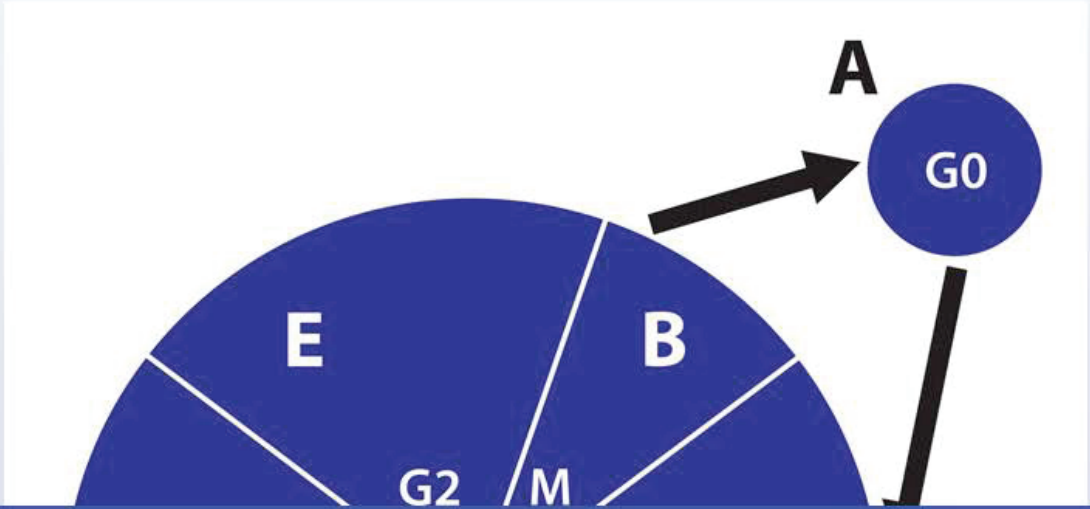
(Choices F, G, and H) Diclofenac, ibuprofen, and indomethacin are NSAIDs that **reversibly** inhibit COX-1 and COX-2.

Educational objective:
Aspirin (acetylsalicylic acid) is a nonsteroidal anti-inflammatory drug (NSAID) that irreversibly inhibits cyclooxygenase-1 and -2 (COX-1 and -2) enzymes via acetylation. In contrast, other NSAIDs (eg, diclofenac, ibuprofen, indomethacin) reversibly inhibit COX-1 and COX-2.

References

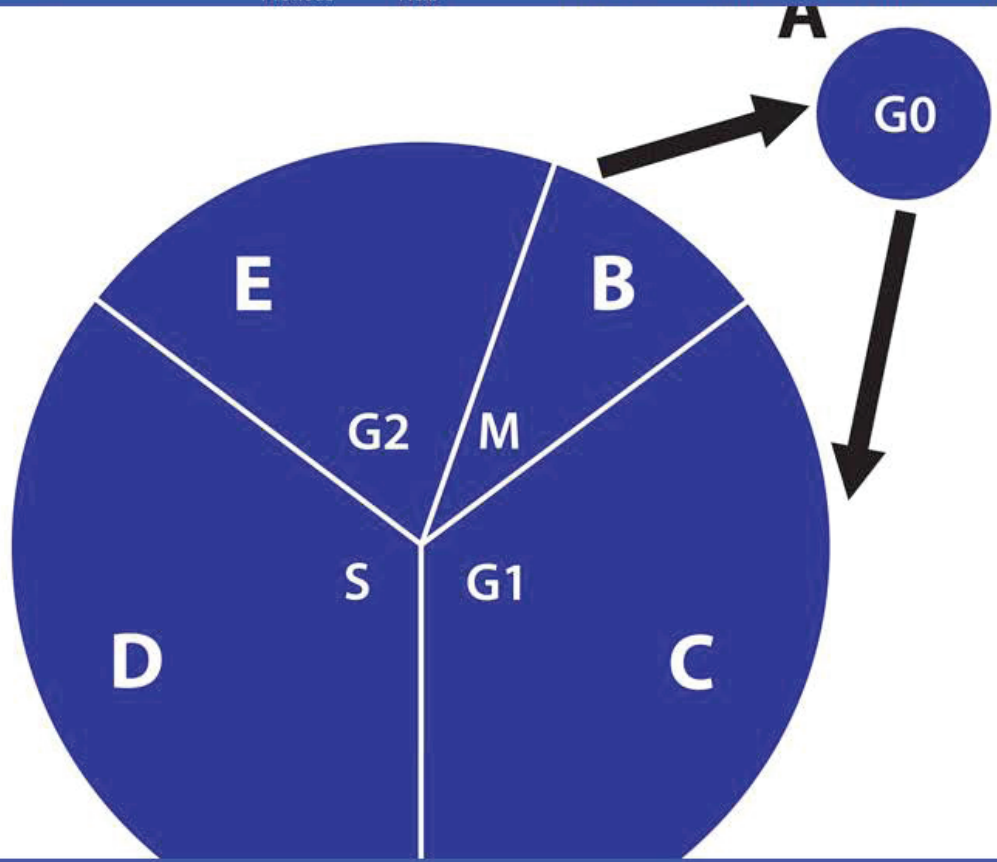
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A 61-year-old man comes to the office due to tingling of his hands and feet. He has a history of diffuse large B cell lymphoma and has received several cycles of systemic chemotherapy with a regimen that includes cyclophosphamide, doxorubicin, and vincristine. Neurologic examination is notable for a symmetric distal neuropathy in a "stocking and glove" distribution. His electrolytes and fasting blood glucose are normal. The drug responsible for this patient's neurologic symptoms causes cell cycle arrest during which of the following stages?

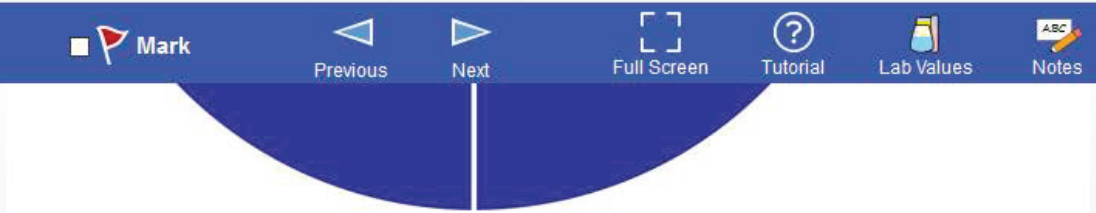


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- A. A (3%)
- ✓ B. B (68%)
- C. C (13%)
- D. D (12%)
- E. E (2%)

Correct

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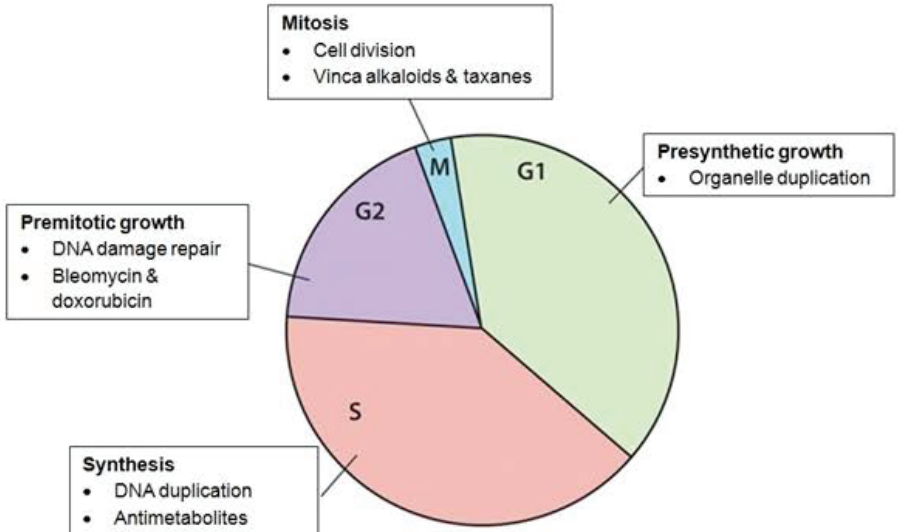
Explanation

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Explanation

Cancer cell cycle



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This patient with diffuse large B cell lymphoma (most common type of **non-Hodgkin lymphoma**) has peripheral neuropathy likely due to vincristine. The **vinca alkaloids** (eg, vincristine, vinblastine) function by **inhibiting microtubule formation**. Specifically, these agents bind to β-tubulin, thereby preventing polymerization of microtubule proteins. This causes cell cycle-specific cytotoxicity during the **M phase** of the cell cycle as the replicated chromosomes are unable to align and subsequently unable to segregate into the daughter cells.

Of the vinca alkaloids, **vincristine** is most classically associated with neurotoxicity, which is often dose-related and most commonly presents as **peripheral neuropathy**. Neurotoxicity likely results from disruption of neuronal microtubules, which are responsible for transporting organelles and other cellular products between the neuronal cell body and the axon terminals.

(Choices A, C, D, and E) The following is a description of the phases of the cell cycle:

- G1: Cells in this phase prepare the building blocks for DNA synthesis.
- G0: This is a resting stage.
- S: DNA replication occurs during this phase. Topoisomerase I and II inhibitors (eg, etoposide, irinotecan), as well as some antimetabolites (eg, methotrexate, 5-fluorouracil), function during this phase.

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phase.

- G2: In this phase, DNA is checked for errors and corrections are made if possible. If corrections cannot be made, then apoptosis will result unless loss-of-function mutations to the genes controlling this process are present, a condition frequently encountered in tumor cells. Chemotherapeutic agents active at this stage include drugs that intercalate with DNA and induce free radical formation. Examples are bleomycin (can cause lung fibrosis) and doxorubicin (can cause cardiomyopathy).
- M: Division occurs during this stage. Vinca alkaloids and taxanes are specific to this phase.

Some chemotherapeutic agents are cell-cycle nonspecific; these include cyclophosphamide, an alkylating agent with side effects that include bone marrow suppression, alopecia, and hemorrhagic cystitis.

Educational objective:

The vinca alkaloids are cell cycle-specific agents that prevent proper separation of chromosomes into daughter cells during the M phase of the cell cycle. The main dose-limiting side effect of vincristine is neurotoxicity, which commonly manifests as peripheral neuropathy.

Pharmacology	Hematology & Oncology	Chemotherapy
Subject	System	Topic

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A 41-year-old previously healthy woman comes to the office due to weakness and easy fatigability. She also has had several episodes of epistaxis and gum bleeding. Physical examination reveals mucosal pallor. Further evaluation demonstrates that the patient has a clonal proliferation of white blood cells containing an abnormal protein. In an experiment, the abnormal cells from the patient are purified and cultured in 2 different plates, one with a vitamin A derivative (plate 1) and the other with control (plate 2). After several days of incubation, cells in plate 1 are well differentiated compared to those in plate 2, and clonal proliferation is inhibited. This patient most likely has which of the following conditions?

A. Acute lymphocytic leukemia (4%)
B. Acute myeloid leukemia (83%)
C. Chronic lymphocytic leukemia (3%)
D. Chronic myeloid leukemia (7%)
E. High-grade non-Hodgkin lymphoma (1%)

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Acute promyelocytic leukemia (APL), type M3 of acute myelogenous leukemia in the French-American-British classification system, results from a **t(15;17) mutation** whereby the gene for retinoic acid receptor alpha (*RARα*) is transferred from chromosome 17 to chromosome 15, where it fuses with the promyelocytic leukemia (*PML*) gene. This leads to the formation of a new gene called ***PML/RARα***. Normally, *RARα* plays a role in the proper differentiation of myeloid precursors, as the receptor interacts with retinoic acid to affect transcription of genes required for maturation. However, the t(15;17) mutation in APML causes transcription repression and produces an **abnormal receptor** that is unable to signal for the differentiation of myeloid precursors at physiologic doses of retinoic acid.

Treatment with **all-trans-retinoic acid** (ATRA), a vitamin A derivative, overcomes this (partly by inducing PML/RARα proteolysis) and stimulates differentiation of myeloblasts into mature granulocytes. ATRA therapy induces remission in about 90% of patients with APL. APL is associated with disseminated intravascular coagulation.

(Choice A) Acute lymphocytic leukemia predominantly affects children. Blast cells positive for the CD10 antigen (CALLA) suggest a good prognosis.

(Choice C) Chronic lymphocytic leukemia is frequently seen in elderly patients. It presents with

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lymphadenopathy, hepatosplenomegaly, and anemia, and has an indolent course. Neoplastic cells resemble mature B lymphocytes.

(Choice D) In chronic myeloid leukemia (also commonly manifesting in elderly patients with fatigue, leukocytosis, and splenomegaly), myeloid precursors in different stages of differentiation proliferate. This disease is caused by a t(9;22) translocation that forms the *BCR-ABL* fusion gene, which codes for an abnormal tyrosine kinase.

(Choice E) Several high-grade non-Hodgkin lymphomas are associated with cytogenetic abnormalities. t(8;14), t(2;8), and t(8;22) are typical for Burkitt lymphoma; these translocations involve the c-*myc* oncogene. Burkitt lymphoma is associated with Epstein-Barr virus infection and classically has a "starry sky" histologic appearance.

Educational objective:
Acute promyelocytic leukemia is the M3 variant of acute myelogenous leukemia. It affects adult patients and may present with disseminated intravascular coagulation. The cytogenetic abnormality t(15;17) leads to formation of the promyelocytic leukemia-retinoic acid receptor alpha (*PML/RARα*) fusion gene, which is unable to signal for proper cellular differentiation, unlike the normal retinoic acid receptor.

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A 9-year-old girl is brought to the emergency department due to prolonged epistaxis. The girl says that she picked her nose immediately before the bleeding started. Her parents decided to bring her to the emergency department after the epistaxis persisted for 20 minutes despite constant compression of the nasal alae. The patient has had frequent nosebleeds that often last >10 minutes. Her family history is significant for a grandfather who had an unspecified bleeding disorder. Given the history of prolonged, recurrent nosebleeds, laboratory tests are ordered, and results are as follows:

Hematocrit	43%
Bleeding time	prolonged
Partial thromboplastin time (PTT)	prolonged
Prothrombin time (PT)	normal
Thrombin time (TT)	normal
D-dimer	normal

Which of the following is the most likely diagnosis?

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Partial thromboplastin time (PTT)	prolonged
Prothrombin time (PT)	normal
Thrombin time (TT)	normal
D-dimer	normal

Which of the following is the most likely diagnosis?

- A. Disseminated intravascular coagulopathy (0%)
- B. Dysfibrinogenemia (0%)
- C. Factor XIII deficiency (4%)
- D. Hemophilia A (9%)
- E. Hemophilia B (3%)
- F. Vitamin K deficiency (1%)
- ✓ G. von Willebrand disease (80%)

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This patient has a normal prothrombin time (PT) and thrombin time (TT) and a **prolonged partial thromboplastin time (PTT)**, indicating a defect in the intrinsic pathway (coagulation factors VIII, IX, XI, or XII). **Bleeding time** is a test of **platelet function** and is prolonged by qualitative and quantitative platelet defects. The term "bleeding time" refers to this particular test and not the duration of bleeding, which can be prolonged from other coagulopathies.

von Willebrand disease (vWD) will cause both a prolonged PTT and bleeding time. von Willebrand factor (vWF) is produced by endothelial cells and megakaryocytes and functions as a **carrier protein for factor VIII** and as a **mediator of platelet adhesion** to the endothelium. Absence of vWF leads to impaired platelet function and coagulation pathway abnormalities. vWD is inherited in an autosomal dominant fashion with variable penetrance and is the **most common heritable bleeding disorder**.

(Choice A) Disseminated intravascular coagulopathy (DIC) is a consumptive coagulopathy most commonly seen in septic shock. PT, PTT, and bleeding time are prolonged, and the D-dimer, a degradation product of cross-linked fibrin, is elevated.

(Choice B) Dysfibrinogenemias are inherited abnormalities in the fibrinogen molecule that can cause excessive bleeding or thrombophilia. TT, PT, and PTT are abnormal in this condition, but bleeding time is unaffected.

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Factor XIII deficiency causes spontaneous or excessive bleeding, but it would not prolong the bleeding time, PT, or PTT.

(Choice D) Hemophilia A is an X-linked hereditary deficiency of factor VIII that causes coagulopathy with a prolonged PTT but shows normal bleeding time.

(Choice E) Hemophilia B is an X-linked hereditary deficiency of factor IX that causes coagulopathy with a prolonged PTT but shows normal bleeding time.

(Choice F) Vitamin K is required for activation of clotting factors II, VII, IX, and X. Vitamin K deficiency causes a coagulopathy that primarily prolongs PT, with PTT prolongation occurring in severe cases. Bleeding time is not affected.

Educational objective:

von Willebrand disease is the most common inherited bleeding disorder. It has an autosomal dominant pattern of inheritance and variable penetrance. Absence of von Willebrand factor leads to impaired platelet function (prolonged bleeding time) and coagulation pathway abnormalities due to decreased factor VIII activity (prolonged partial thromboplastin time).

References

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A 3-year-old boy is brought to the physician with jaundice and pallor. He was adopted and his family history is unknown. Laboratory studies show anemia, reticulocytosis, and increased indirect bilirubin. A peripheral blood smear shows red blood cells without central pallor. This patient is most likely to have which of the following additional findings?

A. Decreased lactate dehydrogenase (4%)
B. Increased haptoglobin (12%)
C. Increased mean corpuscular hemoglobin concentration (59%)
D. Increased mean corpuscular volume (13%)
E. Red blood cell inclusions (10%)

Correct

59% Answered correctly

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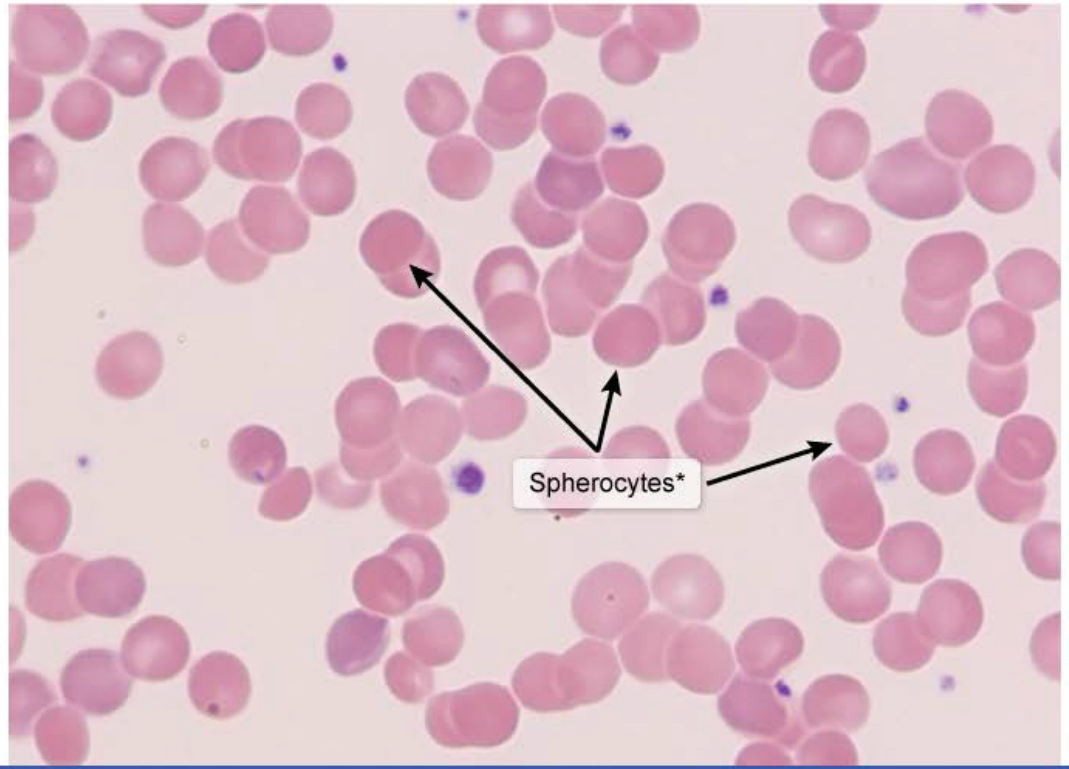
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Explanation

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Hereditary spherocytosis



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*Small erythrocytes without central pallor

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This patient's anemia, reticulocytosis, and increased indirect bilirubin are indicative of hemolytic anemia. His peripheral blood smear shows red blood cells **without central pallor** (ie, spherocytes), which suggests acquired or hereditary **spherocytosis**. Hereditary spherocytosis is caused by defective binding of the red cell cytoskeleton to the plasma membrane due to mutations involving ankyrin, band 3, or spectrin proteins; acquired spherocytosis is most often caused by autoimmune hemolytic anemia. Compared to normal red blood cells, spherocytes are smaller and have a more intensely-staining cytoplasm due to membrane loss and red cell dehydration. The red cell index most specific for spherocytosis is an elevation in **mean corpuscular hemoglobin concentration (MCHC)**.

(Choice A) Lactate dehydrogenase (LDH) is an enzyme present in red blood cells. LDH will be elevated in any cause of hemolytic anemia.

(Choice B) Haptoglobin is an acute phase reactant that combines with free hemoglobin in the circulation to preserve body iron stores and prevent tissue damage. Haptoglobin levels decrease in any form of hemolytic anemia (even with extravascular hemolysis, as some free hemoglobin will spill into the blood stream).

(Choice D) The mean corpuscular volume (MCV) is generally normal to low in hereditary spherocytosis

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(Choice A) Lactate dehydrogenase (LDH) is an enzyme present in red blood cells. LDH will be elevated in any cause of hemolytic anemia.

(Choice B) Haptoglobin is an acute phase reactant that combines with free hemoglobin in the circulation to preserve body iron stores and prevent tissue damage. Haptoglobin levels decrease in any form of hemolytic anemia (even with extravascular hemolysis, as some free hemoglobin will spill into the blood stream).

(Choice D) The mean corpuscular volume (MCV) is generally normal to low in hereditary spherocytosis.

(Choice E) Red blood cell inclusions, such as Howell-Jolly bodies (DNA) and Pappenheimer bodies (iron), are occasionally associated with hemolytic anemia but are more commonly associated with splenectomy and sideroblastic anemia, respectively.

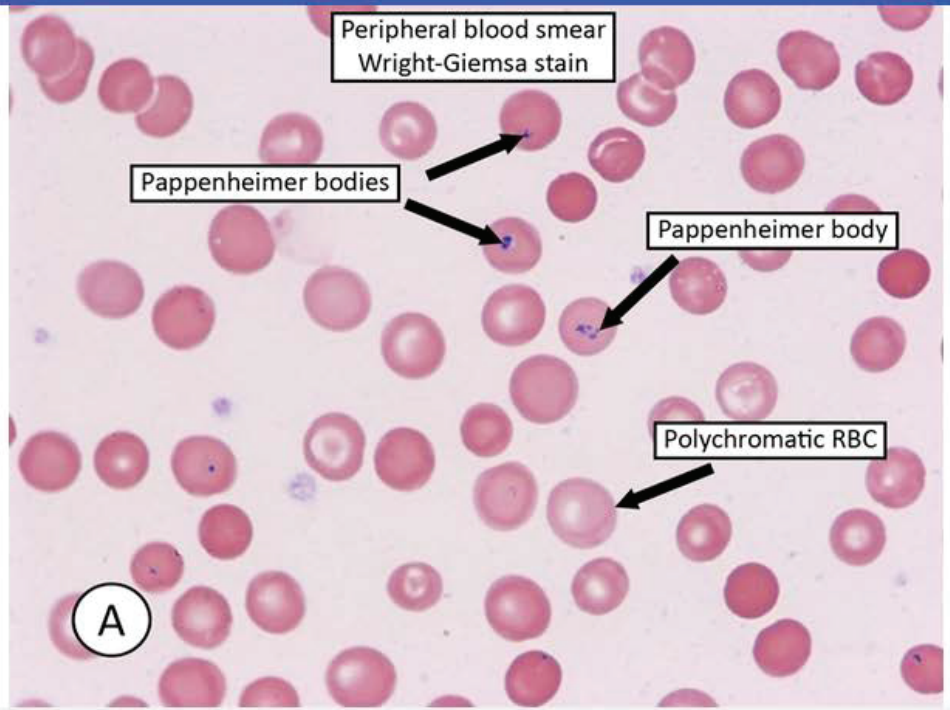
Educational objective:
In spherocytosis, mean corpuscular hemoglobin concentration (MCHC) is increased due to mild dehydration of the red blood cell. Markers of hemolysis are often evident and include elevated lactate dehydrogenase, reticulocytosis, and decreased haptoglobin.

Pathophysiology	Hematology & Oncology	Hereditary spherocytosis

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(Choice A) Lactate dehydrogenase (LDH) is an enzyme present in red blood cells. LDH will be elevated

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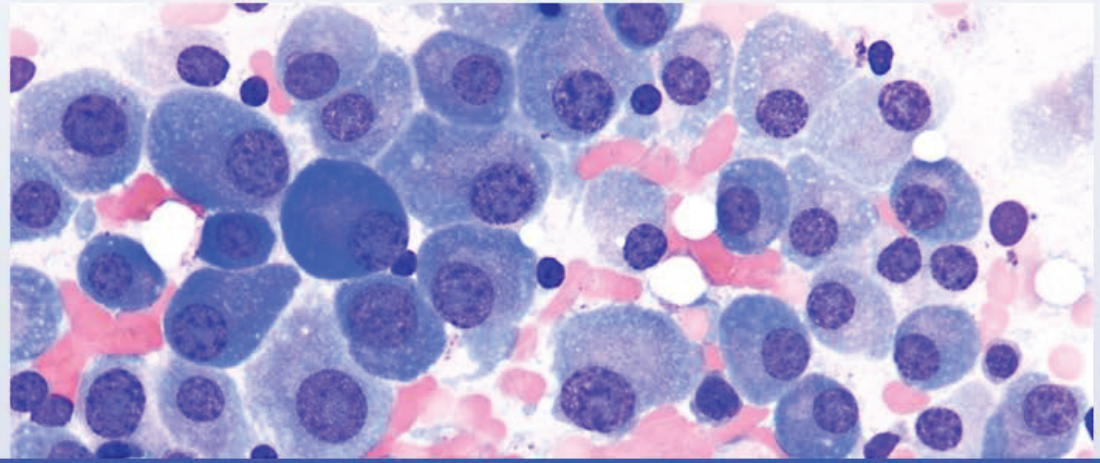


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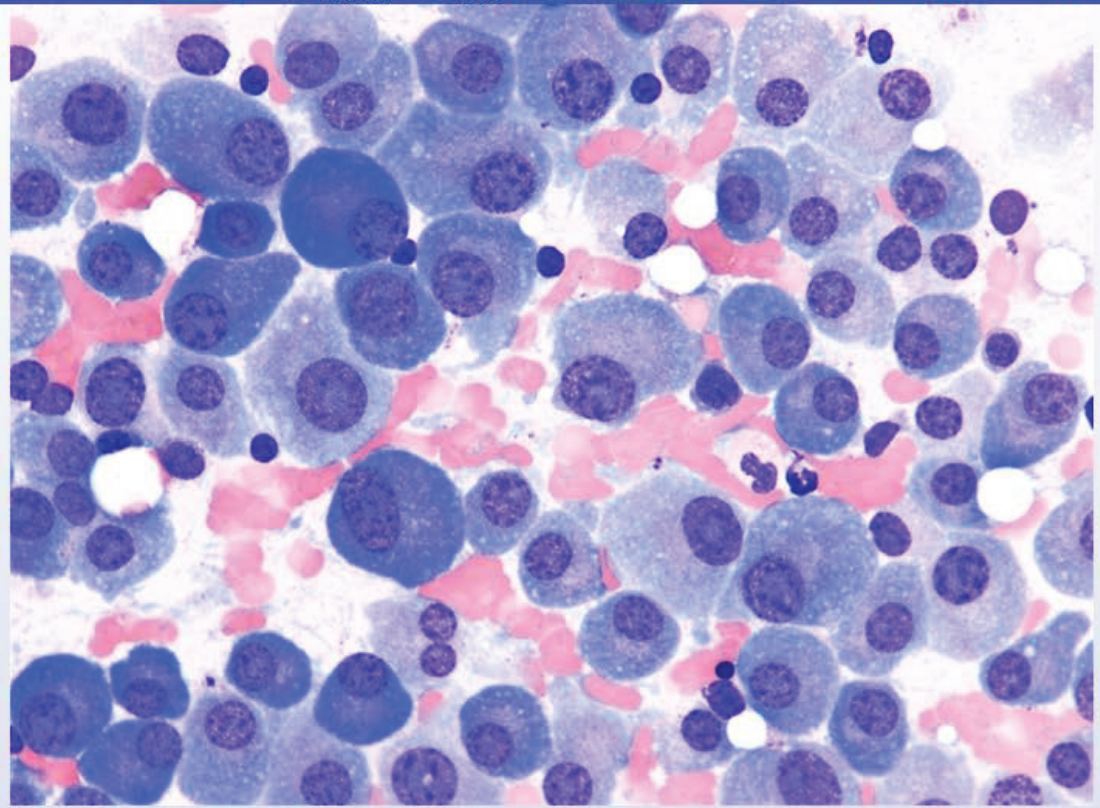
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A 68-year-old woman comes to the office due to recurrent bacterial sinusitis, pneumonia, and urinary tract infections over the past several months. The patient has no prior medical conditions or history of severe infections in childhood. She does not use tobacco, alcohol, or illicit drugs. Temperature is 36.6 C (97.9 F), blood pressure is 130/76 mm Hg, and pulse is 72/min. On physical examination, the lungs are clear to auscultation, heart sounds are normal, and the abdomen is soft and nontender with no hepatosplenomegaly. Laboratory testing reveals normocytic normochromic anemia. Bone marrow aspirate shows an increased number of cells, as shown below.



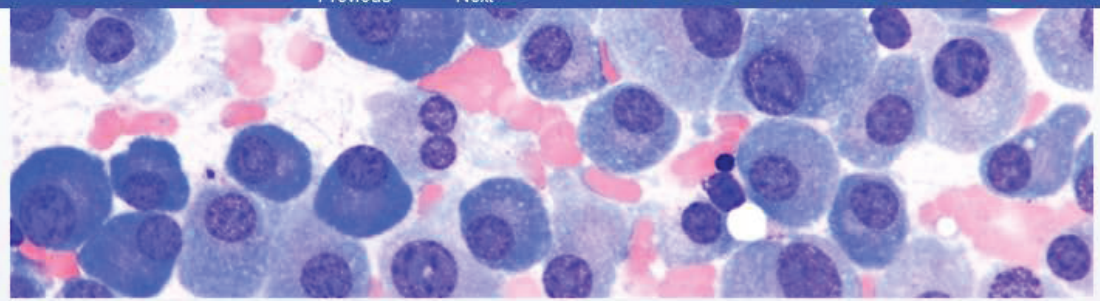
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Which of the following is the most likely cause of this patient's increased susceptibility to infections?

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Which of the following is the most likely cause of this patient's increased susceptibility to infections?

A. Aberrant lysosomal transport and fusion in leukocytes (6%)

B. Decreased production of functional immunoglobulins (77%)

C. Defective adhesion and transmigration of leukocytes (7%)

D. Impaired formation of membrane attack complex (2%)

E. Impaired phagocytic ability to generate superoxide (5%)

Correct

77%

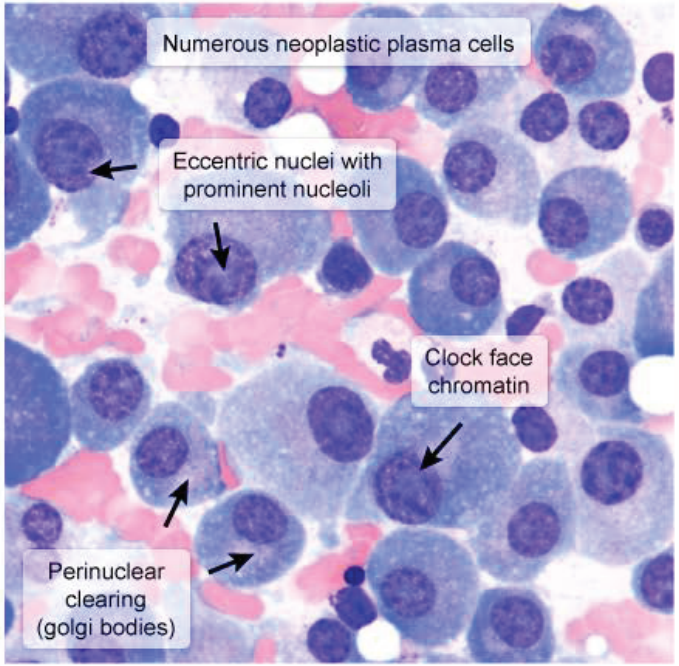
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Plasma cell neoplasm



Multiple myeloma: >10% bone marrow plasma cells

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This patient's bone marrow aspirate has numerous **plasma cells**, which are distinguished by the presence of abundant basophilic cytoplasm, **perinuclear paleness** (large Golgi apparatus), and nuclei with "**clock-face**" (peripheral) chromatin. The presence of >10% plasma cells in the bone marrow raises strong suspicion for **multiple myeloma** (MM).

In MM, neoplastic plasma cells crowd the bone marrow, leading to impairments in normal hematopoiesis. B-cell development is particularly affected, which reduces plasma cell diversity and **limits the generation of targeted immunoglobulins** against infectious agents. Therefore, patients with MM have increased risk of **recurrent bacterial infections**, particularly of the urinary tract, lungs, and sinuses. Although patients with MM have high levels of circulating monoclonal immunoglobulin, monoclonal immunoglobulin does not provide immunity against a diverse range of pathogens.

MM is also associated with normocytic anemia (due to ineffective erythropoiesis), bone pain (due to osteolytic lesions), hypercalcemia, and renal insufficiency (due to clogging of the tubules with immunoglobulin light chains).

(Choice A) Chediak-Higashi syndrome is a rare autosomal recessive disorder that causes abnormal lysosomal fusion and transport. Although it is associated with recurrent bacterial infections and hematologic malignancies, most cases are identified in early childhood, and patients generally have

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(Choice A) Chediak-Higashi syndrome is a rare autosomal recessive disorder that causes abnormal lysosomal fusion and transport. Although it is associated with recurrent bacterial infections and hematologic malignancies, most cases are identified in early childhood, and patients generally have hypopigmentation and progressive neurologic dysfunction.

(Choice C) Leukocyte adhesion deficiency is an inherited disorder associated with defective adhesion and transmigration of leukocytes from the vasculature to tissues. Patients typically have recurrent bacterial infections that begin in early childhood. It is not associated with excessive plasma cells in the bone marrow.

(Choice D) Terminal complement deficiency (C5-C9) prevents the formation of the membrane attack complex and dramatically increases the risk of recurrent infection with *Neisseria* species; patients are usually healthy otherwise and have no abnormalities in the bone marrow.

(Choice E) Chronic granulomatous disease is a genetic disorder associated with severe bacterial and fungal infections due to impaired ability of phagocytes to generate reactive oxygen species (oxidative burst). Most cases present in early childhood, and plasma cell effacement of the bone marrow would not be seen.

Educational objective:

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(Choice E) Chronic granulomatous disease is a genetic disorder associated with severe bacterial and fungal infections due to impaired ability of phagocytes to generate reactive oxygen species (oxidative burst). Most cases present in early childhood, and plasma cell effacement of the bone marrow would not be seen.

Educational objective:
Multiple myeloma is associated with the clonal proliferation of plasma cells in the bone marrow. This prevents normal B-cell lymphogenesis and increases the risk of bacterial infection due to decreased production of normal immunoglobulins.

Immunology	Hematology & Oncology	Multiple myeloma
Subject	System	Topic

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A 60-year-old man comes to the emergency department due to 10 days of worsening cough, shortness of breath, and right-sided chest pain. The patient also has had low-grade fever, fatigue, and unspecified weight loss. A month ago, he was hospitalized for 2 days due to right lower lobe pneumonia. Although oral antibiotics were prescribed at discharge, he did not get the prescription filled because his symptoms had improved. Temperature is 38.2 C (100.8 F), blood pressure is 116/70 mm Hg, pulse is 104/min, and respirations are 18/min. Physical examination is notable for decreased breath sounds at the right lung base. Chest imaging reveals loculated pleural fluid on the right side. Laboratory analysis reveals the following:

Hemoglobin	10.4 g/dL	
Mean corpuscular volume	96 μm^3	
Platelets	580,000/mm^3	
Leukocytes	17,200/mm^3	(80% neutrophils)

Blood cell counts were normal a month ago at the time of hospital discharge. Which of the following is the most likely underlying cause of this patient's increased platelet count?

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following:

Hemoglobin	10.4 g/dL
Mean corpuscular volume	96 μm^3
Platelets	580,000/mm^3
Leukocytes	17,200/mm^3 (80% neutrophils)

Blood cell counts were normal a month ago at the time of hospital discharge. Which of the following is the most likely underlying cause of this patient's increased platelet count?

A. ~~Autonomous clonal proliferation of megakaryocytes~~ (9%)
B. ~~Chronic hypoxia-induced erythropoietin release~~ (11%)
C. Cytokine-mediated megakaryocyte proliferation and maturation (63%)
D. ~~Decreased platelet sequestration by the spleen~~ (7%)
E. ~~Increased platelet production from extramedullary hematopoiesis~~ (7%)

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This patient with partially treated pneumonia developed progressive pulmonary symptoms and pleural effusion indicating likely empyema. Although laboratory results were normal when he was discharged a month ago, his complete blood cell count now reveals signs of ongoing infection (neutrophilic leukocytosis) and inflammation (anemia, thrombocytosis).

Infections are associated with the release of **inflammatory cytokines** (eg, IL-6, TNF-alpha) from activated immune cells. Elevated circulating concentrations of IL-6 stimulate the liver to increase production of **thrombopoietin**, which triggers **megakaryocyte proliferation and maturation** in the bone marrow. The subsequent increase in serum platelet count is called reactive thrombocytosis because it is a secondary process that typically resolves when the infection is adequately treated. **Reactive thrombocytosis** is seen in a wide range of inflammatory (eg, malignancy, rheumatologic disease, burns) and noninflammatory (eg, iron deficiency, hemolysis, blood loss, postsplenectomy) conditions and is the most common cause of elevated platelet count in all age groups.

Elevated circulating levels of inflammatory cytokines also trigger the liver to generate hepcidin, which down-regulates iron absorption in the gut and iron release by the reticuloendothelial system; this frequently leads to concurrent **anemia of chronic disease** (normocytic anemia) due to reduced iron availability for reticulocytosis.

(Choices A and E) Essential thrombocythemia, a myeloproliferative disorder characterized by the

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(Choices A and E) Essential thrombocythemia, a myeloproliferative disorder characterized by the autonomous clonal proliferation of megakaryocytes, is marked by thrombocytosis, vasomotor symptoms (eg, dizziness), and increased risk of thrombosis. Primary myelofibrosis is a chronic myeloproliferative disorder characterized by significant extramedullary hematopoiesis (eg, hepatosplenomegaly); it can occasionally be associated with thrombocytosis. It is quite unlikely that this patient developed a myeloproliferative disorder in the month since he was admitted to the hospital; it is far more likely that he has reactive thrombocytosis due to his ongoing infection.

(Choice B) Chronic hypoxemia (eg, chronic obstructive pulmonary disease) can trigger the release of erythropoietin from interstitial cells in the kidneys, leading to increased erythrocytosis and subsequent polycythemia. This would not significantly affect platelet count.

(Choice D) Patients with congestive splenomegaly often have thrombocytosis due to reduced platelet sequestration in the spleen. However, it is far more likely that this patient has reactive thrombocytosis due to empyema.

Educational objective:
Reactive thrombocytosis is the most common cause of elevated platelet count in all age groups. It is generally caused by high levels of inflammatory cytokines (eg, IL-6), which prompt the liver to release

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(Choice D) Patients with congestive splenomegaly often have thrombocytosis due to reduced platelet sequestration in the spleen. However, it is far more likely that this patient has reactive thrombocytosis due to empyema.

Educational objective:
Reactive thrombocytosis is the most common cause of elevated platelet count in all age groups. It is generally caused by high levels of inflammatory cytokines (eg, IL-6), which prompt the liver to release thrombopoietin. Reactive thrombocytosis is seen in chronic infection, rheumatologic disease, and burns; it can also occur with hemolysis and iron deficiency anemia.

Pathology	Hematology & Oncology	Thrombocytosis
Subject	System	Topic

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A 43-year-old Caucasian female complaining of reduced energy and fatigue is found to have hypochromic, microcytic anemia. Her past medical history is significant for stable angina treated with metoprolol and aspirin. Iron supplementation is prescribed. Several weeks later, a peripheral blood smear demonstrates numerous enlarged red blood cells that appear blue on Wright-Giemsa stain. The bluish color of these red blood cells is best explained by the presence of which of the following?

A. Hemoglobin precipitates (26%)
B. Nuclear membrane (12%)
C. Ribosomal RNA (44%)
D. Histones (5%)
E. Mitochondria (10%)
F. Golgi apparatus (1%)

Correct
44%
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This patient suffers from hypochromic, microcytic anemia most likely caused by iron deficiency. Iron-deficient individuals on replacement therapy should experience hemoglobin level increases of approximately 2 g/dL per week for the first three weeks. This increase in hemoglobin results from enhanced erythropoiesis and the accelerated release of both mature red blood cells (RBCs) and reticulocytes into the bloodstream.

The reticulocyte is an immature RBC that is slightly larger and bluer than a mature RBC. It lacks a cell nucleus but retains a basophilic, reticular (mesh-like) network of residual ribosomal RNA. The ribosomal RNA appears blue microscopically after the application of the Wright-Giemsa stain.

After spending a day or so in the bloodstream, the reticulocytes are transformed into mature red blood cells that have a lifespan of approximately 120 days.

(Choices A, B, D, E, and F) The blue color of the reticulocyte is not caused by hemoglobin precipitates, nuclear membranes, histones, mitochondria, or the Golgi apparatus.

Educational Objective:
Increased bone marrow erythropoiesis results in an accelerated release of immature red blood cells (reticulocytes) into the bloodstream. Reticulocytes contain bluish cytoplasm and reticular precipitates of

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Educational Objective:
Increased bone marrow erythropoiesis results in an accelerated release of immature red blood cells (reticulocytes) into the bloodstream. Reticulocytes contain bluish cytoplasm and reticular precipitates of residual ribosomal RNA.

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A 35-year-old man is brought to the emergency department after collapsing in his garage. He recently bought a classic 1960s convertible and was repairing it when he collapsed. The patient was inside the garage but had the door half-open. He lost consciousness after working on the car for 2 hours with the engine running. The patient has no known medical problems and takes no medications. He does not use tobacco, alcohol, or illicit drugs. Which of the following best reflects the combination of findings that would have been expected in an arterial blood sample taken when the patient lost consciousness?

	Carboxyhemoglobin (%)[normal = 0-2]	PaO_2 (mm Hg)[normal = 85-100]	Methemoglobin (%)[normal = 0-1]	
A.	2	95	30	(4%)
B.	35	45	1	(27%)
C.	35	45	25	(15%)
D.	40	95	1	(44%)
E.	40	95	25	(7%)

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Carbon monoxide (CO) is a colorless, odorless gas product of the combustion of carbon-containing compounds. CO poisoning can occur after exposure to automobile exhaust (especially in older cars without catalytic converters), fire smoke, or improperly vented natural gas appliances. CO has 2 major effects on oxygen delivery to tissues:

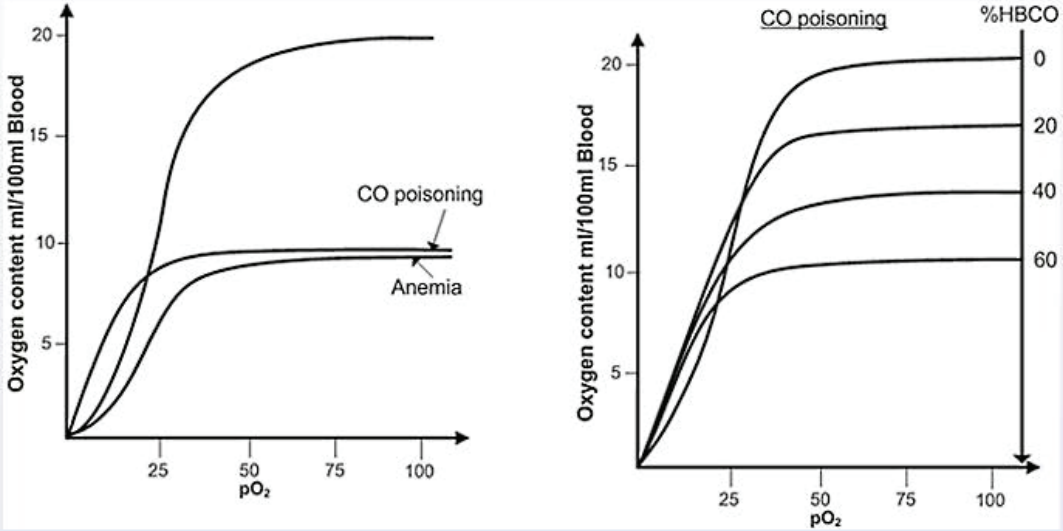
1. CO binds to hemoglobin with an affinity approximately 250 times that of oxygen, reducing the number of heme binding sites available to oxygen. As a result, levels of CO-bound hemoglobin, represented by **carboxyhemoglobin** (HBCO), **increase**. By decreasing the fraction of hemoglobin available for oxygen binding, CO decreases the oxygen-carrying capacity and **oxygen content** of blood, but **not** the amount of oxygen **dissolved** in plasma, reflected by the partial pressure of oxygen (PaO_2).
2. CO poisoning causes a **leftward** shift of the hemoglobin-oxygen dissociation curve, reflecting a decreased tendency for oxygen to unload in the tissues.

CO's effects on arterial blood oxygen content are seen in the graphs below, which show the lower oxygen content with CO poisoning (similar to anemia) and the leftward shift of the dissociation curve that becomes increasingly more pronounced at increasingly higher HBCO concentrations (this does not occur with anemia).



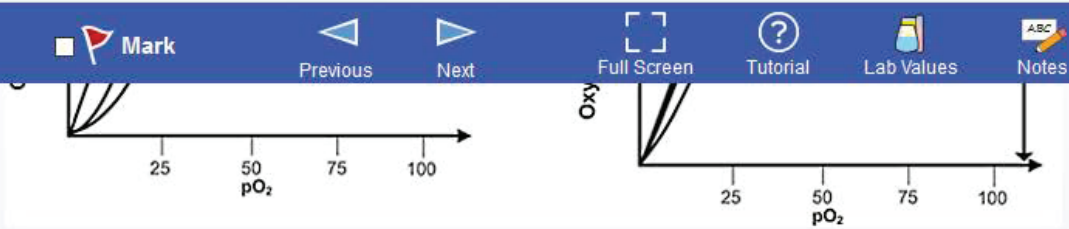
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anemia).



(Choices A, B, C, and E) CO poisoning does not affect PaO_2 and it does not cause methemoglobinemia. Methemoglobin is formed when the Fe^{2+} (ferrous iron) in heme is oxidized to Fe^{3+} (ferric iron). Methemoglobinemia results from drug exposures (ie, dapsone, nitrites) as well as enzyme deficiencies and hemoglobinopathies.

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(Choices A, B, C, and E) CO poisoning does not affect PaO_2 and it does not cause methemoglobinemia. Methemoglobin is formed when the Fe^{2+} (ferrous iron) in heme is oxidized to Fe^{3+} (ferric iron). Methemoglobinemia results from drug exposures (ie, dapsone, nitrites) as well as enzyme deficiencies and hemoglobinopathies.

Educational objective:

Carbon monoxide (CO) binds to hemoglobin with much higher affinity than oxygen, thereby preventing oxygen binding to hemoglobin. It also reduces oxygen unloading from hemoglobin in the tissues. CO poisoning increases carboxyhemoglobin concentrations but does not affect the partial pressure of oxygen and does not precipitate methemoglobinemia.

Physiology	Hematology & Oncology	Carbon monoxide poisoning
Subject	System	Topic

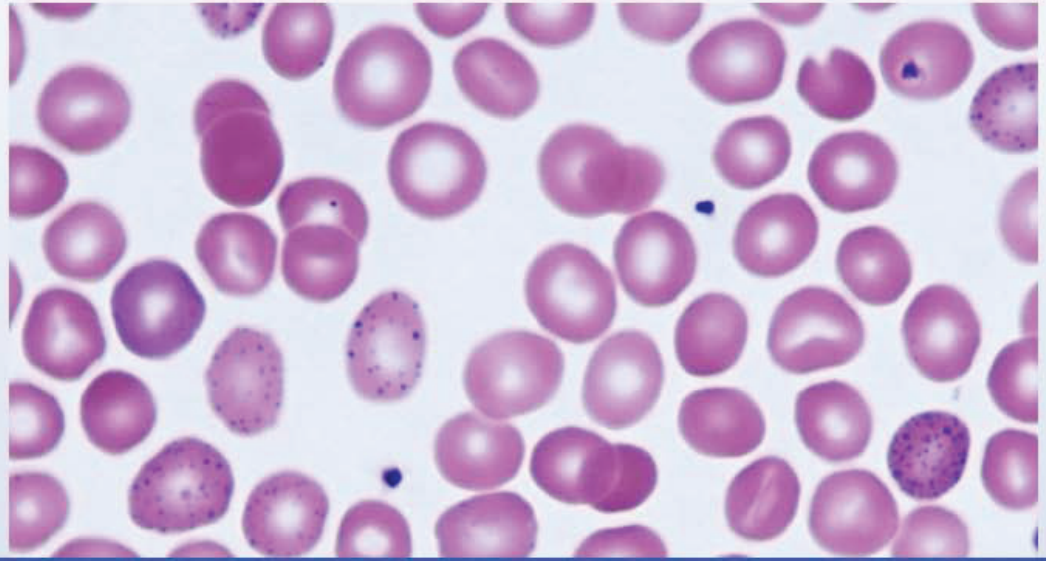
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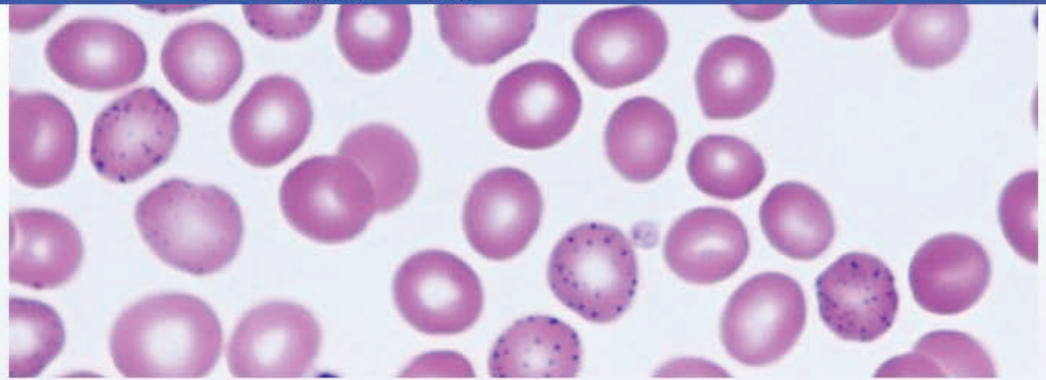
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A 23-year-old man comes to the emergency department due to 4 days of cramping abdominal pain. He has been feeling weak for the past 2 weeks. He tried over-the-counter antacids without relief. He is an industrial laborer with no significant medical history or known allergies. The patient's parents have hypertension, and his siblings are healthy. Temperature is 37.1 C (98.8 F). Physical examination is unremarkable. The patient's peripheral blood smear is shown on the image below.



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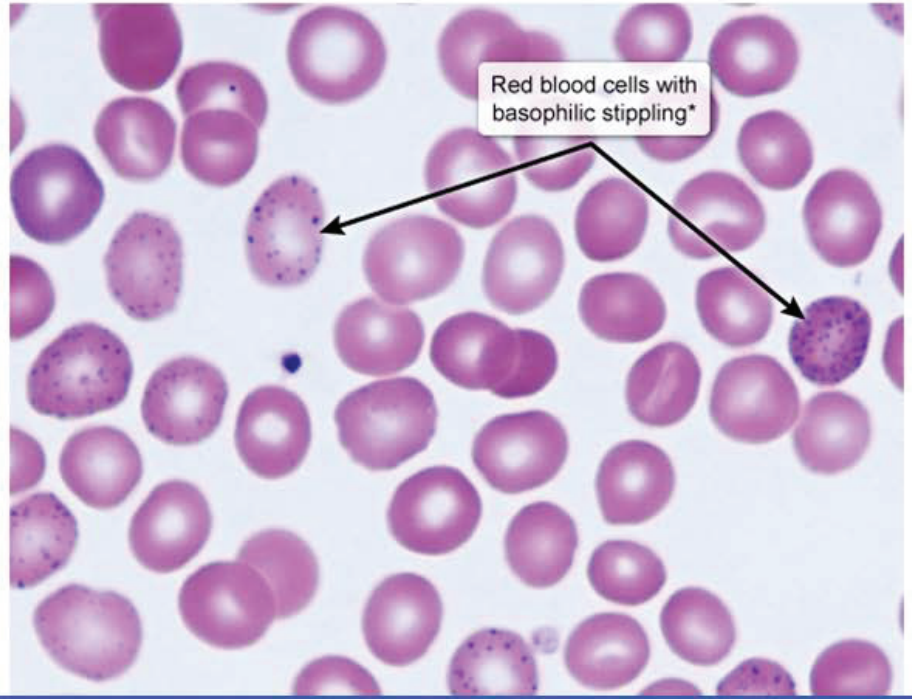
Which of the following is the most likely cause of this patient's symptoms?

- A. Acute intermittent porphyria (5%)
- B. Acute leukemia (0%)
- C. Atrophic gastritis (1%)
- ✓ D. Metal poisoning (90%)
- E. Non-Hodgkin lymphoma (0%)
- F. Poor nutrition (0%)

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Basophilic stippling



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*Precipitated ribosomes seen in thalassemia, alcohol use disorder, and lead poisoning

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This patient likely has **lead poisoning**. In the United States, lead poisoning (plumbism) is typically a pediatric condition that results from children ingesting lead-containing **paint** chips. However, lead poisoning can also occur in adults. Affected individuals are usually **miners** or industrial workers (especially those in battery manufacturing) who inhale particulate lead while working. Adults with lead poisoning present with weakness, **abdominal pain**, and constipation. In severe cases, there may be **neurologic** manifestations (eg, headache, cognitive symptoms, peripheral neuropathy). On physical examination, patients may have **blue "lead lines"** at the junction of the teeth and gingivae.

The classic diagnostic finding on peripheral blood smear is coarse **basophilic stippling** on a background of hypochromic microcytic anemia. Basophilic stippling results from the abnormal degradation of ribosomal RNA (due to lead-induced inhibition of a nucleotidase). The hypochromic microcytic anemia results from inhibition of δ-aminolevulinate dehydratase (δ-ALA dehydratase) and the resultant reduced incorporation of iron into heme. The net effect of these defects is decreased hemoglobin synthesis.

(Choice A) Acute intermittent porphyria can cause attacks of abdominal pain (without abdominal tenderness) due to autonomic neuropathy. Erythropoiesis is not affected, and the peripheral blood smear is normal.

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(Choice B) Myeloblasts containing cytoplasmic Auer rods on peripheral blood smear are a characteristic finding of acute myelogenous leukemia.

(Choice C) The autoimmune destruction of gastric parietal cells and/or intrinsic factor cause atrophic (autoimmune) gastritis, which can lead to pernicious anemia due to vitamin B_{12} malabsorption.

(Choice E) Non-Hodgkin lymphoma can invade the bone marrow, causing myelophthisic anemia. A peripheral blood smear would show leukoerythroblastosis (immature granulocytes and nucleated teardrop-shaped erythrocytes).

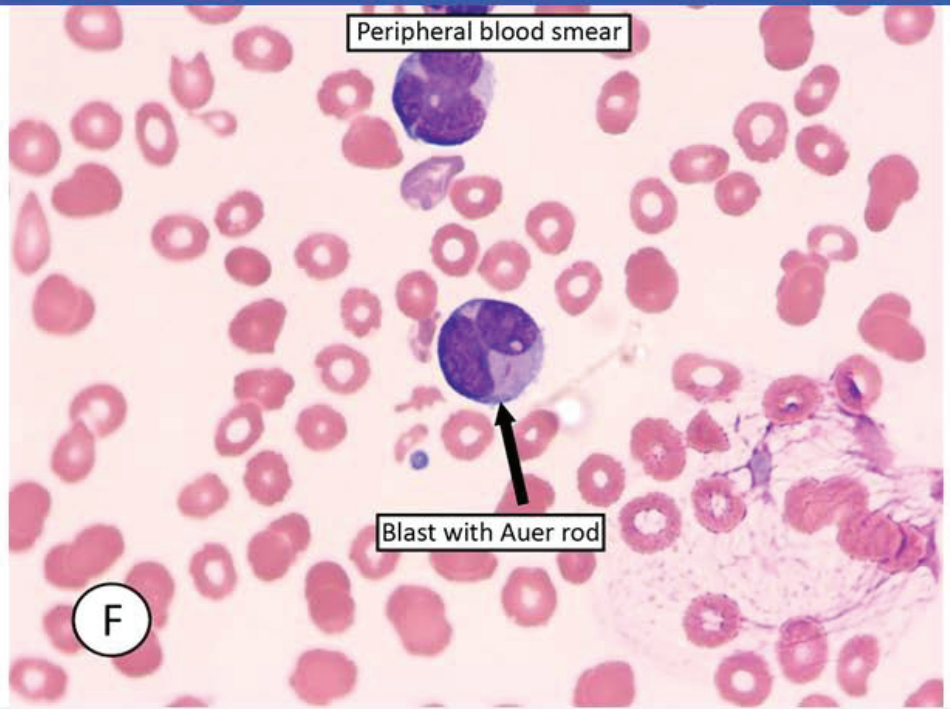
(Choice F) Malnutrition may lead to folate deficiency or, more rarely, vitamin B_{12} deficiency. Deficiencies of either vitamin cause megaloblastic anemia, with hypersegmented neutrophils and large erythrocytes on peripheral blood smear.

Educational objective:
Coarse erythrocyte basophilic stippling and microcytic hypochromic anemia are common peripheral blood smear findings in lead poisoning. High-risk groups include young children ingesting paint chips and industrial workers inhaling particulate lead.

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A 17-year-old girl comes to the office for follow-up on anemia. She has taken iron supplements regularly since being diagnosed with iron deficiency anemia 3 months ago. However, the patient still feels fatigued and does not think that the supplements have improved her symptoms. She has occasional gingival bleeding when brushing her teeth. Menses occur every 27-28 days and last 7-8 days with heavy flow, sometimes requiring her to change pads every hour. Platelet count is normal. Further evaluation reveals that the patient's platelets do not agglutinate appropriately in response to ristocetin. When normal plasma is added to the solution of patient platelets and ristocetin, appropriate platelet agglutination occurs. Which of the following is most likely deficient in this patient?

A. Glycoprotein Ib receptors (6%)
B. Glycoprotein IIb-IIIa receptors (13%)
C. Hageman factor (3%)
D. Thromboxane A2 (2%)
E. Von Willebrand factor (73%)

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GP = glycoprotein; vWF = von Willebrand factor.

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Von Willebrand factor (vWF) is an important hemostatic glycoprotein (GP) synthesized by endothelial cells and megakaryocytes. Following endothelial damage, vWF **binds GP Ib receptors** on the platelet membrane and mediates **platelet adhesion** to subendothelial collagen. Deficiency of vWF impairs platelet adhesion and can lead to easy bruising and **prolonged mucocutaneous bleeding** (eg, gingival bleeding, heavy menses).

Laboratory workup in vWF deficiency reveals a normal platelet count and an **abnormal ristocetin cofactor assay**. The ristocetin cofactor assay measures in-vitro, vWF-dependent platelet agglutination (indicative of impaired platelet adhesion in-vivo). Ristocetin activates GP Ib receptors on platelets and makes them available for vWF binding; when the vWF level is decreased, there is **poor platelet agglutination in the presence of ristocetin**. When normal plasma that contains vWF is added, appropriate platelet agglutination occurs.

VWF also serves as a **carrier for factor VIII** to prolong its half-life, and vWF deficiency can lead to functional deficiency of factor VIII that further contributes to bleeding complications. PTT may be normal or prolonged depending on the degree of factor VIII impairment.

Combined oral contraceptives are often used for treatment of menorrhagia due to vWF deficiency. Patients

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Combined oral contraceptives are often used for treatment of menorrhagia due to vWF deficiency. Patients can also be treated with desmopressin, which stimulates vWF release from endothelium.

(Choice A) Bernard-Soulier syndrome (hereditary deficiency of GP Ib receptors) is characterized by thrombocytopenia, enlarged platelets, and mucocutaneous bleeding. Platelet agglutination to ristocetin will be abnormal and, because the deficiency is with GP Ib receptors and not vWF, the addition of normal plasma will not correct the agglutination.

(Choice B) Hereditary deficiency of GP IIb/IIIa receptors occurs in Glanzmann thrombasthenia, which manifests with mucocutaneous bleeding. Platelet agglutination in response to ristocetin is normal because the levels of vWF and GP Ib receptors are normal.

(Choice C) Congenital deficiency of factor XII (Hageman) causes marked PTT prolongation; however, it does not cause clinical bleeding complications. Instead, patients may have a tendency for thromboembolic complications for unclear reasons.

(Choice D) Thromboxane A2 deficiency is associated with aspirin treatment due to irreversible inactivation of cyclooxygenase in platelets. The major effect is on GP IIb/IIIa-mediated platelet aggregation rather than GP Ib-mediated platelet adhesion; therefore, platelet agglutination to ristocetin is normal.

Educational objective:

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the levels of vWF and GP Ib receptors are normal.

(Choice C) Congenital deficiency of factor XII (Hageman) causes marked PTT prolongation; however, it does not cause clinical bleeding complications. Instead, patients may have a tendency for thromboembolic complications for unclear reasons.

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Educational objective:

Following endothelial damage, von Willebrand factor (vWF) binds glycoprotein Ib receptors on platelets to mediate platelet adherence. The ristocetin cofactor assay measures platelet agglutination via binding of glycoprotein Ib receptors to vWF; it will be abnormal in vWF deficiency but will correct with the addition of normal (vWF-containing) plasma.

References

- Diagnosis and management of von Willebrand disease: guidelines for primary care.
- Of von Willebrand factor and platelets.

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A 53-year-old man comes to the physician due to frequent headaches and dizziness. He has a history of hypertension and peptic ulcer disease. His medications include daily chlorthalidone and antacids as needed. The patient's temperature is 37 C (98.6 F), blood pressure is 146/92 mm Hg, pulse is 89/min, and respirations are 16/min. His BMI is 26 kg/m^2. Physical examination shows facial plethora and moderate splenomegaly. Laboratory results are as follows:

Complete blood count	
Hemoglobin	21.5 g/dL
Hematocrit	64%
Erythrocytes	7.6 million/mm^3
Mean corpuscular volume	90 µm^3
Mean corpuscular hemoglobin	31 pg/cell
Mean corpuscular hemoglobin concentration	33% Hb/cell
	14.0% (n = 10.3%-

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Mean corpuscular hemoglobin	31 pg/cell
Mean corpuscular hemoglobin concentration	33% Hb/cell
Red blood cell distribution width	14.0% (n = 10.3%-14.1%)
Platelets	545,000/mm^3
Leukocytes	15,500/mm^3

This patient most likely has a mutation in which of the following types of proteins?

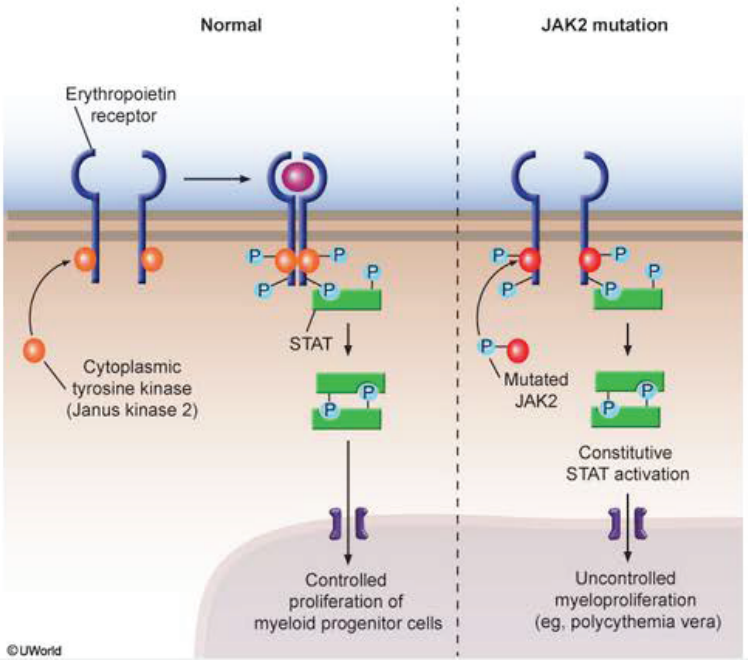
- A. Cytoplasmic tyrosine kinase (33%)
- B. Growth-stimulating transcription factor (25%)
- C. Intrinsic receptor tyrosine kinase (28%)
- D. Tumor suppressor protein (5%)
- E. Vascular growth factor (6%)

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Polycythemia vera



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This patient most likely has **polycythemia vera**, a myeloproliferative disorder characterized by uncontrolled erythrocyte production. Patients frequently present with nonspecific symptoms (eg, headache, weakness, diaphoresis), **aquagenic pruritus**, **facial plethora** (reddish complexion), and **splenomegaly**. Associated conditions include peptic ulcer disease (altered mucosal blood flow due to increased viscosity) and gouty arthritis (higher red cell turnover). Laboratory studies show **increased erythrocyte mass**, thrombocytosis, leukocytosis, and low erythropoietin levels. Erythrocyte indices are usually normal.

Polycythemia vera is caused by abnormal transduction of erythropoietin growth signals. The erythropoietin receptor has no intrinsic kinase activity and must interact with **Janus kinase 2** (JAK2), a **cytoplasmic (non-receptor) tyrosine kinase**, to initiate downstream signaling. Virtually all patients with polycythemia vera have a mutation in JAK2 that causes constitutive activation of its kinase domain, resulting in clonal proliferation of myeloid cells. JAK2 mutations have also been implicated in essential thrombocythemia, primary myelofibrosis, and other myeloproliferative disorders.

(Choice B) Burkitt lymphoma is characterized by translocation of the c-*myc* oncogene on chromosome 8 to the Ig heavy chain region on chromosome 14. This results in constitutive expression of c-Myc, a growth-stimulating transcription factor.

(Choice C) Intrinsic receptor tyrosine kinases are receptors with intrinsic kinase activity that

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to the Ig heavy chain region on chromosome 14. This results in constitutive expression of c-Myc, a growth-stimulating transcription factor.

(Choice C) Intrinsic receptor tyrosine kinases are receptors with intrinsic kinase activity that autophosphorylate and induce a downstream signaling cascade upon ligand binding. Examples include the receptors for insulin, insulin-like growth factor, and epidermal growth factor. Mutations causing excessive epidermal growth factor receptor activity occur in many solid tumors.

(Choice D) Mutations of the p53 tumor suppressor are associated with Li-Fraumeni syndrome, an autosomal dominant disorder with predisposition to a variety of cancers, particularly sarcomas and tumors of the breast, brain, and adrenal cortex.

(Choice E) Expression of vascular endothelial growth factor (VEGF) is required for tumor angiogenesis, a critical step in the process of tumor growth and metastasis. VEGF upregulation occurs in the vast majority of cancers.

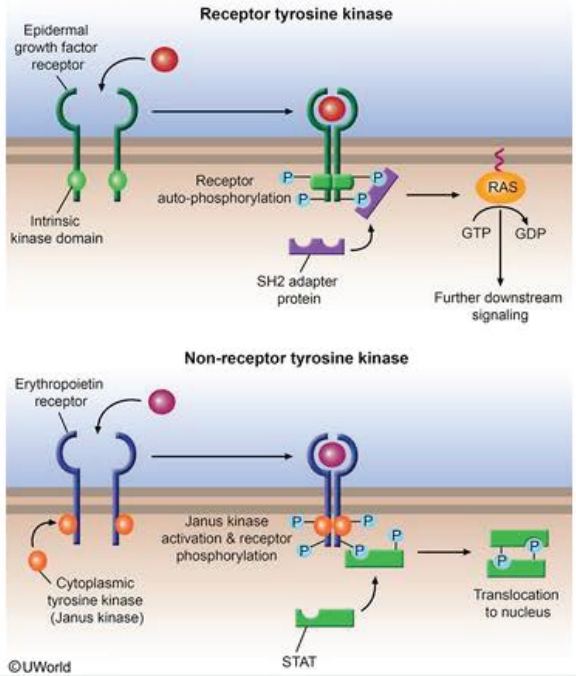
Educational objective:
Polycythemia vera is a myeloproliferative disorder characterized by uncontrolled erythrocyte production. Virtually all patients with polycythemia vera have a mutation in JAK2, a non-receptor (cytoplasmic) tyrosine kinase associated with the erythropoietin receptor.

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to the Ig heavy chain region on chromosome 14. This results in constitutive expression of c-Myc, a growth-

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Receptor vs non-receptor tyrosine kinases



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A 62-year-old woman is being evaluated for worsening anemia. The patient was admitted to the hospital 2 days ago due to acute pyelonephritis. She has been treated with intravenous ceftriaxone, and her fever and urinary symptoms have gradually improved. The patient has no history of anemia and has had no symptoms of urinary or gastrointestinal bleeding. Laboratory results are as follows:

	On admission	2 days later
Hemoglobin	12.3 g/dL	8.4 g/dL
Platelets	285,000/mm^3	300,000/mm^3
Leukocytes	14,800/mm^3	10,000/mm^3
Serum creatinine	1.0 mg/dL	0.8 mg/dL
Serum bilirubin	0.8 mg/dL	2.4 mg/dL
Prothrombin time	12 sec	11 sec

Her antibiotics are changed to a different medication class, and the patient is discharged a few days later. At a follow-up office visit 2 weeks later, her laboratory abnormalities have resolved. Which of the following is the most likely cause of this patient's anemia?

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Serum bilirubin	0.8 mg/dL	2.4 mg/dL
Prothrombin time	12 sec	11 sec

Her antibiotics are changed to a different medication class, and the patient is discharged a few days later. At a follow-up office visit 2 weeks later, her laboratory abnormalities have resolved. Which of the following is the most likely cause of this patient's anemia?

- ✓ A. Antibody-mediated erythrocyte injury (58%)
- B. Cytokine-mediated iron dysregulation (4%)
- C. ~~Drug-induced myelosuppression~~ (6%)
- D. ~~Erythrocyte enzyme deficiency~~ (24%)
- E. ~~Microthrombi-induced erythrocyte injury~~ (5%)

Correct

58% Answered correctly

02 mins, 02 secs Time Spent

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Drug-induced immune-mediated hemolytic anemia	
Pathogenesis	• Drug coats erythrocytes → IgG binding → splenic destruction of RBCs (extravascular hemolysis) • Drug triggers immune complexes → complement-mediated destruction of RBCs (intravascular hemolysis)
	• Sudden onset (within hours of exposure) • Anemia: fatigue, pallor, dyspnea • Hemolysis: jaundice, dark urine, abdomen/back pain

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Manifestations	exposure) • Anemia: fatigue, pallor, dyspnea • Hemolysis: jaundice, dark urine, abdomen/back pain ◦ ↑ Reticulocytes, indirect bilirubin & LDH ◦ ↓ Haptoglobin ◦ Spherocytes on peripheral blood smear ◦ + Direct Coombs test (anti-IgG, anti-C3)
Treatment	• Discontinue offending drug

LDH = lactate dehydrogenase; **RBC** = red blood cell.

This patient developed anemia and hyperbilirubinemia during treatment with ceftriaxone, raising strong

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LDH = lactate dehydrogenase; **RBC** = red blood cell.

This patient developed anemia and hyperbilirubinemia during treatment with ceftriaxone, raising strong suspicion for **drug-induced hemolytic anemia**. The most common triggers of drug-induced hemolysis are anti-inflammatory medications, penicillins, and cephalosporins (eg, **ceftriaxone**). Although the mechanism of erythrocyte injury (eg, oxidative, complement mediated) varies depending on the medication, penicillins and cephalosporins typically cause hemolysis by binding to the erythrocyte surface, which creates a **hapten for IgG attachment**. Antibody-coated erythrocytes are then partially or wholly phagocytized by splenic macrophages, leading to **extravascular hemolysis**.

Hemolysis is often associated with symptomatic anemia (eg, fatigue, pallor) and signs of hyperbilirubinemia (eg, jaundice, dark urine). Laboratory evaluation will typically reveal **elevated indirect bilirubin** (heme breakdown product), elevated lactate dehydrogenase (intracellular enzyme), reticulocytosis (increased immature RBCs), and lowered haptoglobin (binds free hemoglobin). The diagnosis is confirmed with the **direct antiglobulin (Coombs) test**, which detects IgG or C3 (a complement fragment) on the erythrocyte surface. Because hemolysis is triggered by the direct binding of the penicillin or cephalosporin to the erythrocyte membrane, **cessation of the offending drug** eliminates the antibody target and generally leads to complete resolution of symptoms within days.

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generally leads to complete resolution of symptoms within days.

(Choice B) Anemia of chronic disease is caused by cytokine-mediated iron dysregulation. Although chronic infection (eg, viral hepatitis, tuberculosis) is a common trigger, anemia of chronic disease is gradual in onset and is not associated with hyperbilirubinemia (no RBC lysis).

(Choice C) Certain antibiotics (eg, sulfa medications, chloramphenicol) are associated with myelosuppression. However, these medications generally cause pancytopenia, not isolated anemia; in addition, hyperbilirubinemia is not seen.

(Choice D) Glucose-6-phosphate dehydrogenase (G6PD) deficiency is marked by hemolysis in the setting of oxidative stress due to infection, oxidizing medication, or oxidative foods. Although this patient has an infection, ceftriaxone is not an oxidizing medication. In addition, G6PD deficiency is X-linked; therefore, symptoms are less common in women.

(Choice E) Severe infections can trigger disseminated intravascular coagulation, a consumptive coagulopathy associated with anemia due to erythrocyte injury from microvascular thrombi. However, these patients have prolonged coagulation times and thrombocytopenia.

Educational objective:

Penicillins and cephalosporins are common triggers for drug-induced hemolytic anemia because they can

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(Choice D) Glucose-6-phosphate dehydrogenase (G6PD) deficiency is marked by hemolysis in the setting of oxidative stress due to infection, oxidizing medication, or oxidative foods. Although this patient has an infection, ceftriaxone is not an oxidizing medication. In addition, G6PD deficiency is X-linked; therefore, symptoms are less common in women.

(Choice E) Severe infections can trigger disseminated intravascular coagulation, a consumptive coagulopathy associated with anemia due to erythrocyte injury from microvascular thrombi. However, these patients have prolonged coagulation times and thrombocytopenia.

Educational objective:
Penicillins and cephalosporins are common triggers for drug-induced hemolytic anemia because they can bind to the erythrocyte surface and act as haptens for IgG attachment. Subsequent clearance of IgG-coated erythrocytes by splenic macrophages leads to hemolytic anemia. Withdrawal of the offending drug usually leads to complete resolution of symptoms.

Pharmacology	Hematology & Oncology	Hemolytic anemia
Subject	System	Topic

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A 34-year-old woman comes to the office after her sister was diagnosed with breast cancer. She has no nipple discharge, breast lumps, or discomfort. Breast examination is normal. Her sister was found to have a multiple base pair insertion affecting exon 11 of the *BRCA1* gene that leads to a frameshift mutation. A screening test to evaluate for a similar insertion mutation in the patient's *BRCA1* gene is performed. The test uses polymerase chain reaction (PCR) to amplify the target exon and gel electrophoresis to assess the size of the exon compared to the wild-type allele. Which of the following must be known in order to perform the amplification part of this analysis?

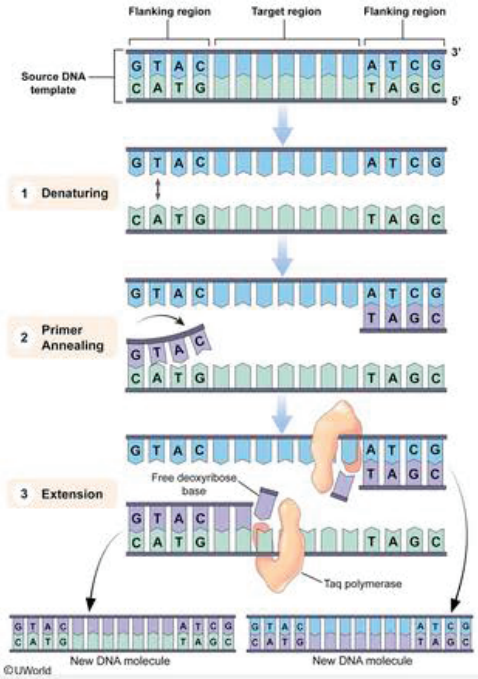
A. Restriction enzyme susceptibility sites within the target exon (14%)
B. The amino acid sequence of the abnormal BRCA1 protein (10%)
C. The cDNA nucleotide sequence (13%)
D. The complete nucleotide sequence of the target exon (12%)
E. The nucleotide sequence of the regions flanking the target exon (49%)

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Polymerase chain reaction



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Polymerase chain reaction (PCR) is used to **amplify** small fragments of DNA (eg, genes, exons, noncoding regions) by repeated replication. Several elements are required for PCR. The first is a source **DNA template** that includes the target region to be amplified (eg, *BRCA1* exon 11) as well as flanking sequences adjacent to the target region. The oligonucleotide sequence of these flanking regions must be known in order to make the **primers** necessary to start PCR. However, the exact nucleotide sequence of the target region does **not** need to be known **(Choice D)**. A thermostable **DNA polymerase** (not denatured at high temperatures) is then used to replicate the DNA template from a pool of supplied **deoxynucleotide triphosphates** using the following 3 steps:

1. **Denaturing**: Thermal separation of the DNA template is accomplished by exposing the sample to high temperatures
2. **Annealing**: Primers combine with the denatured, single-stranded flanking ends of the target region when the temperature is lowered
3. **Elongation**: DNA polymerase forms new daughter DNA strands in the 5' to 3' direction, starting from the 3' end of each primer

These steps are repeated to obtain millions of copies of the target DNA segment in a short period of time (exponential amplification).

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(exponential amplification).

(Choice A) Restriction sites are cleaved by specific endonucleases and can be used to identify polymorphisms within variant alleles on gel electrophoresis (restriction fragment length polymorphism analysis). However, knowing the restriction enzyme susceptibility sites within the target region is not necessary for PCR amplification.

(Choice B) In PCR, only DNA segments are amplified and studied; proteins are not involved. Proteins can be analyzed using Western blots, but even then, exact amino acid sequences do not need to be known.

(Choice C) Complementary DNA (cDNA) is produced by the reverse transcriptase enzyme using mRNA as a template in reverse transcriptase PCR; it is not used in regular PCR. cDNA can be used to express eukaryotic proteins in prokaryotes by transferring the cDNA into the genome of a recipient organism.

Educational objective:
Polymerase chain reaction is used to amplify small fragments of DNA (eg, genes, exons, noncoding regions) by repeated replication. It requires primers that are complementary to the regions of DNA flanking the segment of interest. Thermostable DNA polymerase, deoxynucleotide triphosphates, and a source DNA template strand are also necessary.

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An 8-year-old boy with a one-week history of fever and throat pain is brought to the emergency department with severe dyspnea, tachypnea, and inspiratory stridor. He has also experienced worsening dysphagia with solid foods over the last two weeks. Laboratory evaluation reveals many immature hematopoietic cells (blasts) in the peripheral blood smear. The neoplastic cells causing this patient's condition normally give rise to which of the following?

- A. B-lymphocytes (44%)
- B. T-lymphocytes (38%)
- C. ~~Monocytes~~ (8%)
- D. ~~Erythrocytes~~ (7%)
- E. ~~Platelets~~ (0%)

Incorrect
Correct answer
B

38%
Answered correctly

01 min, 49 secs
Time Spent

11/05/2020
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Blast cells in the peripheral blood are strongly suggestive of leukemia. The most common pediatric malignancy is acute lymphoblastic leukemia (ALL). The neoplastic cells of ALL arise from lymphocytic precursors that are of either pre-B or pre-T lineage.

Clinical manifestations of ALL include fever, fatigue, pallor, petechiae, and bleeding. Leukemic spread can cause lymphadenopathy, hepatosplenomegaly, and bone pain. T-cell ALL is more likely to present with a large anterior mediastinal mass that can compress the great vessels, causing superior vena cava syndrome. The mediastinal mass can also compress the esophagus causing dysphagia, while compression of the trachea may lead to dyspnea and stridor. This patient's clinical presentation is therefore most suggestive of T-cell ALL, which most commonly affects males in late childhood through young adulthood.

Because pre-B and pre-T lymphoblasts can look identical on peripheral blood smear, immunohistochemical staining is used to differentiate the two cell lineages. Both lineages contain TdT (an antigen of lymphocyte precursors). Cell surface markers for pre-B lymphoblasts include CD10+, CD 19+, and CD20+; while pre-T lymphoblasts express CD2+, CD3+, CD4+, CD5+, CD7+, and CD8+.

(Choice A) B-cell ALL is responsible for approximately 70-80% of all cases of ALL, whereas T-cell ALL

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lymphoblasts express CD2+, CD3+, CD4+, CD5+, CD7+, and CD8+.

(Choice A) B-cell ALL is responsible for approximately 70-80% of all cases of ALL, whereas T-cell ALL accounts for 15-17% of all cases of ALL. B-cell ALL manifests with fever, malaise, bleeding, bone pain, and hepatosplenomegaly. Generally, B-cell ALL is not associated with symptoms of mediastinal compression.

(Choice C) Acute myeloid leukemia (AML) subtypes M4 and M5 arise from monocytic precursors. This is rarely seen in children and usually does not present as a mediastinal mass, though extramedullary disease is not an uncommon finding.

(Choice D) The rare AML M6 subtype arises from erythroid precursors and typically affects elderly patients.

(Choice E) The rare AML M7 subtype arises from primitive megakaryoblasts and is associated with t(1;22) and Down syndrome in children.

Educational objective:
Acute lymphoblastic leukemia (ALL) is the most common malignancy of childhood. B-cell ALL is responsible for approximately 70-80% of all cases of ALL, whereas T-cell ALL accounts for 15-17% of all

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compression.

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(Choice E) The rare AML M7 subtype arises from primitive megakaryoblasts and is associated with t(1;22) and Down syndrome in children.

Educational objective:
Acute lymphoblastic leukemia (ALL) is the most common malignancy of childhood. B-cell ALL is responsible for approximately 70-80% of all cases of ALL, whereas T-cell ALL accounts for 15-17% of all cases of ALL. T-cell ALL often presents as a mediastinal mass that can cause respiratory symptoms, dysphagia, or superior vena cava syndrome.

Pathology	Hematology & Oncology	Acute lymphoblastic leukemia
Subject	System	Topic

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A 14-year-old girl with sickle cell disease is admitted to the hospital due to fever for 2 days. Temperature is 38 C (100.4 F), blood pressure is 120/80 mm Hg, pulse is 120/min, and respirations are 18/min. Examination shows no abnormalities. Laboratory studies reveal:

Complete blood count	
Hemoglobin	10 g/dL
Mean corpuscular volume	86 μm^3
Reticulocytes	2%
Platelets	240,000/mm^3
Leukocytes	14,000/mm^3

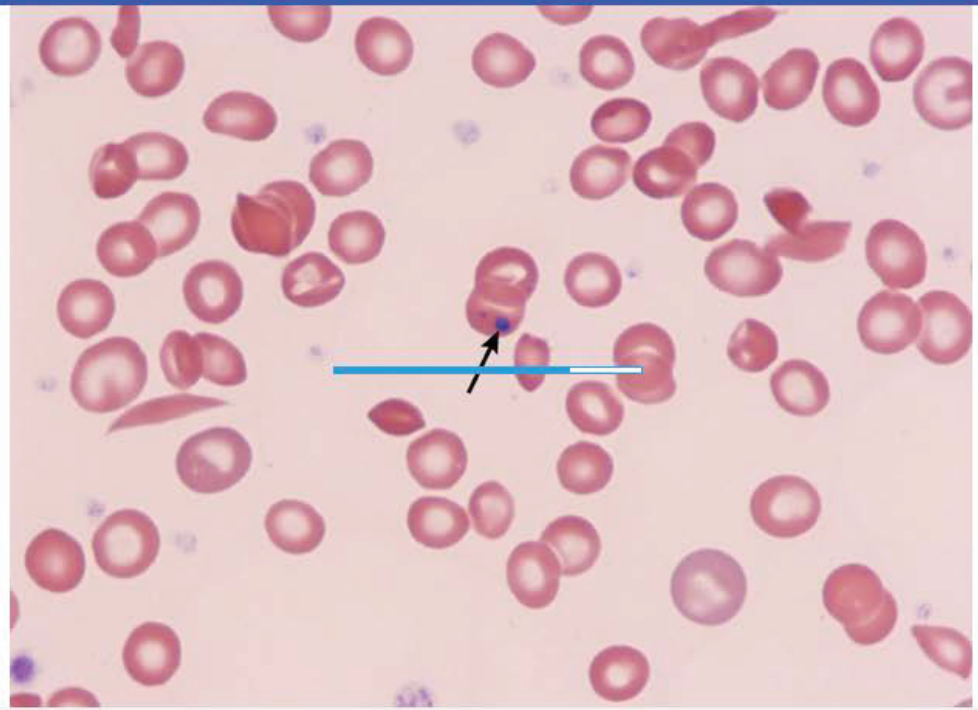
Blood cultures are obtained, and appropriate pharmacotherapy is initiated. Her peripheral blood smear is shown in the exhibit. The smear findings indicated by the arrow most likely reflect which of the following processes?

A. Bone marrow suppression (3%)

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Reticulocytes	2%
Platelets	240,000/mm^3
Leukocytes	14,000/mm^3

Blood cultures are obtained, and appropriate pharmacotherapy is initiated. Her peripheral blood smear is shown in the exhibit. The smear findings indicated by the arrow most likely reflect which of the following processes?

A. Bone marrow suppression (3%)
B. Intracellular parasitic infection (6%)
C. Leukemic infiltration (1%)
D. Splenic dysfunction (83%)
E. Toxic granulations (4%)

Correct

83%

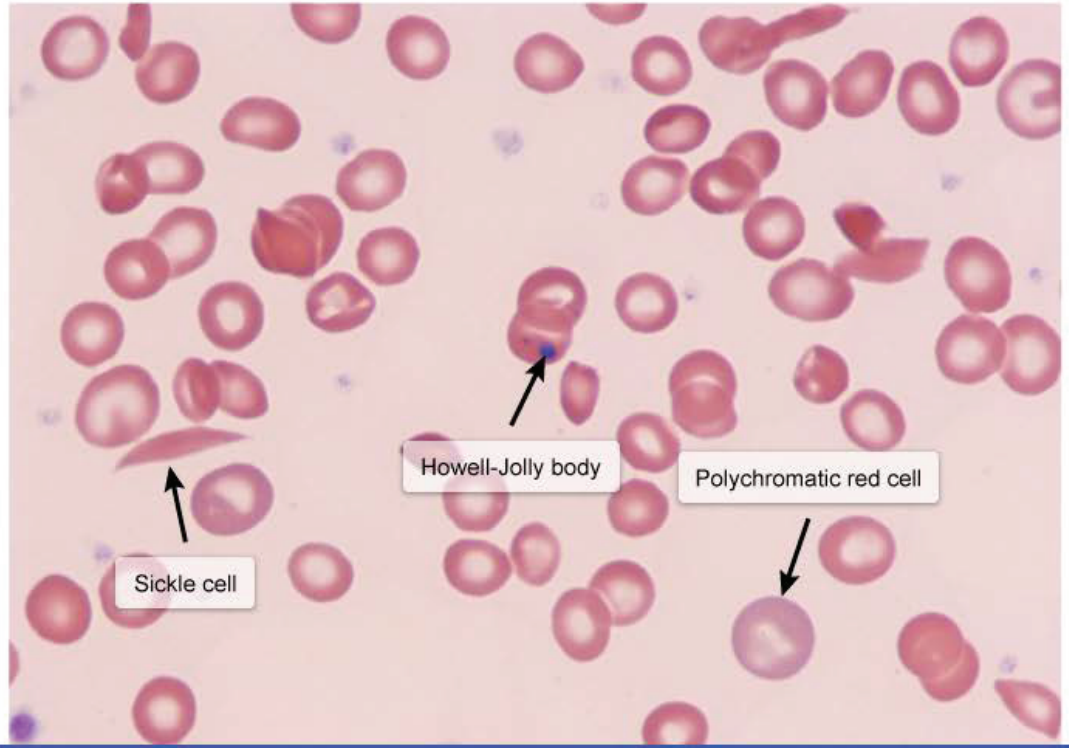
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Peripheral blood smear



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This patient's peripheral smear shows a **Howell-Jolly body**, a dark-purple **remnant** of a **red blood cell** (RBC) **nucleus** that is normally removed by the spleen. In patients with asplenia, which can be anatomic (eg, splenectomy) or functional (eg, **sickle cell disease** [SCD]), Howell-Jolly bodies are not removed from circulation and are therefore present on peripheral smear. This patient also has sickle-shaped RBCs and polychromasia (indicative of reticulocytosis) on peripheral smear, consistent with her underlying SCD.

A point mutation in the beta-globin gene causes sickling of RBCs and the classic manifestations of SCD, including hemolytic anemia and vasoocclusive episodes. **Recurrent infarction** from the poorly deformable RBCs in the splenic vasculature leads to progressive **splenic dysfunction** with functional asplenia by age 5 in most patients.

Because splenic macrophages are critical in the immune response against **encapsulated bacteria** (eg, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Neisseria meningitidis*), patients with SCD are at increased risk of **potentially fatal infection**. Therefore, fever (with or without leukocytosis) in the setting of SCD warrants hospitalization and empiric antibiotic therapy.

(Choice A) Bone marrow suppression can occur in patients with SCD and parvovirus (eg, aplastic crisis). Expected laboratory findings include acute anemia and absent reticulocytes. This patient's hemoglobin level and mild reticulocytosis (due to chronic hemolysis) are typical of SCD at baseline.

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level and mild reticulocytosis (due to chronic hemolysis) are typical of SCD at baseline.

(Choice B) Unlike in this patient, peripheral smear abnormalities with intraerythrocytic parasites include trophozoites (ring forms) in malaria and babesiosis. In addition, both conditions would present with anemia relative to the patient's baseline.

(Choice C) Peripheral smear in leukemia shows circulating blasts, immature cells with a large nucleus and scant cytoplasm. In addition, abnormalities in two cell lines (eg, leukocytosis and thrombocytopenia) are usually seen.

(Choice E) Toxic granulations are purple cytoplasmic granules in the periphery of neutrophils (not RBCs) that are typically seen with infection.

Educational objective:
Howell-Jolly bodies on peripheral smear reflect splenic dysfunction, which occurs in sickle cell disease due to recurrent infarction of the splenic vasculature. Functional asplenia increases the risk of invasive infection with encapsulated organisms.

References

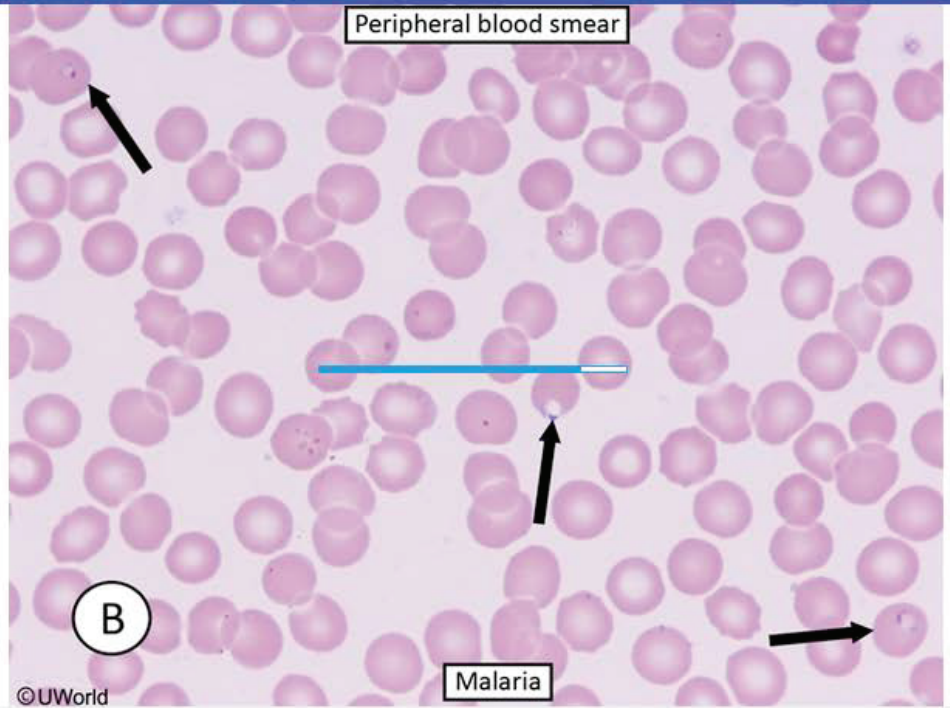
- Insights into determinants of spleen injury in sickle cell anemia.
- Functional hyposplenism.

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level and mild reticulocytosis (due to chronic hemolysis) are typical of SCD at baseline.

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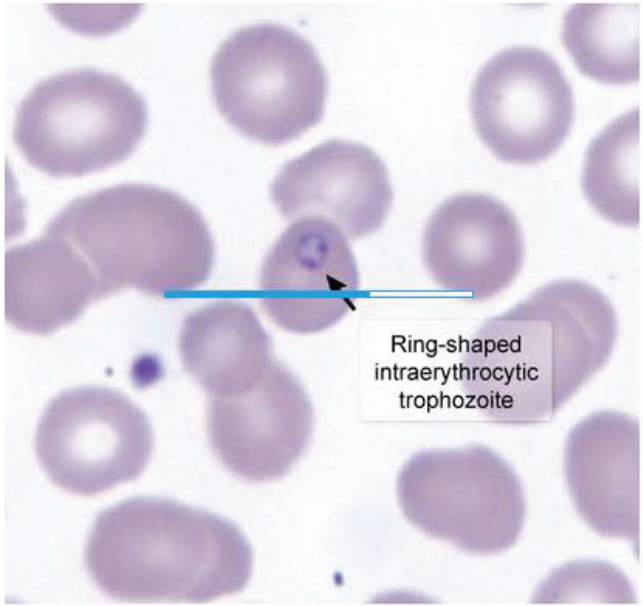
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level and mild reticulocytosis (due to chronic hemolysis) are typical of SCD at baseline.

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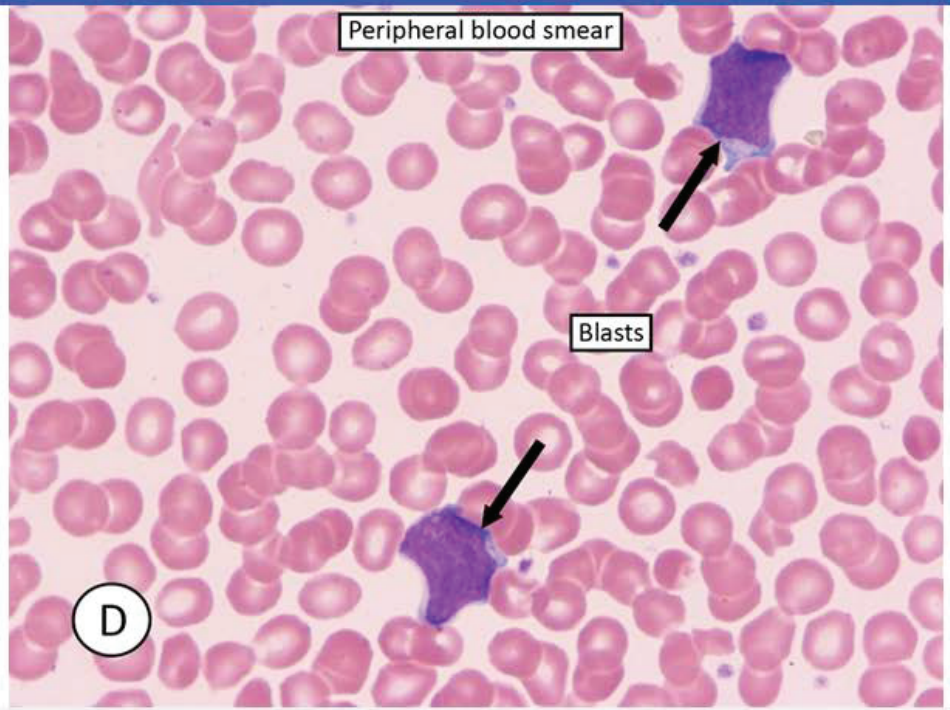
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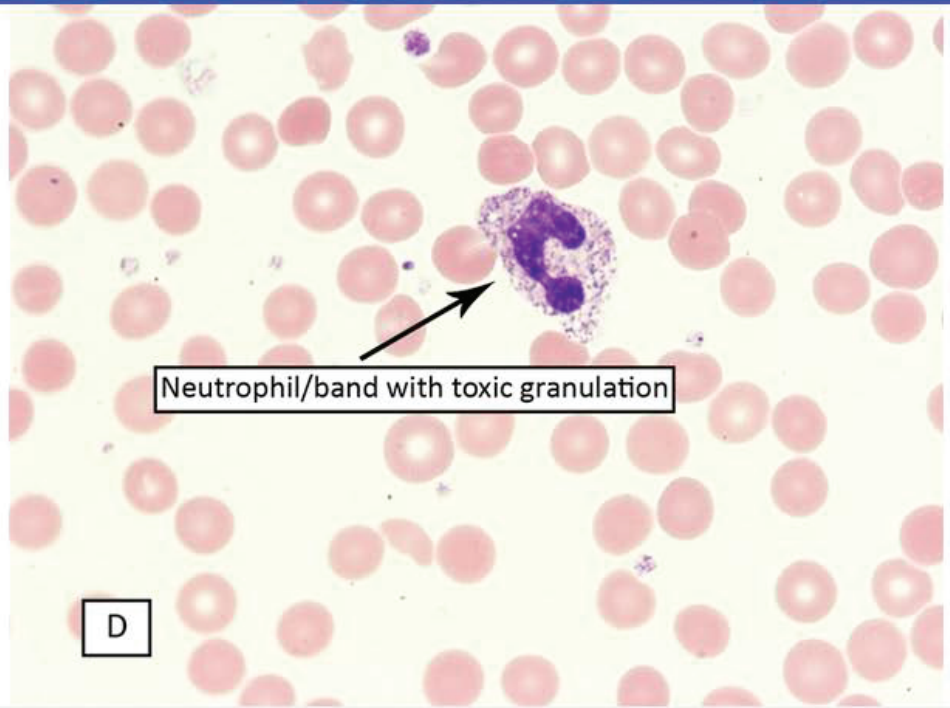
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level and mild reticulocytosis (due to chronic hemolysis) are typical of SCD at baseline.

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• Functional hyposplenism:

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order. Once you click **Proceed to Next Item**, you will not be able to add or change an answer.

A 23-year-old African American man comes to the emergency department due to back and lower extremity pain for 2 days. He has had several similar episodes over the last 15 years that have required hospitalization. His pain is not responsive to over-the-counter analgesics, and review of his prior records shows that he has needed treatment with opioids for adequate pain relief. The patient does not use tobacco, alcohol, or illicit drugs. On physical examination, he has scleral icterus and tenderness over his lower back and long bones of his thighs. Laboratory evaluation shows a hemoglobin level of 6.7 g/dL.

Item 1 of 2

Histopathologic evaluation of this patient's spleen is most likely to reveal which of the following?

- A. Congestion (27%)
- B. Cyst formation (0%)
- ✓ C. Fibrosis and atrophy (63%)
- D. Infiltration (2%)
- E. White pulp hyperplasia (6%)

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This patient with frequent episodes of bony pain likely has **sickle cell disease** (SCD), an autosomal recessive condition characterized by hemolytic anemia and vaso-occlusion. The hemolytic anemia causes **jaundice** (due to unconjugated hyperbilirubinemia) and promotes formation of pigmented gallstones. Vaso-occlusion by sickled red blood cells occurs in various tissues, causing hypoxia and acidosis (vaso-occlusive pain episodes). Microvascular occlusion nearly always affects the spleen due to the trapping of sickle cells by the rigid splenic cords; autoinfarction begins in early childhood and can precipitate splenic sequestration crisis in infants. However, **repeated infarction** eventually leads to significant scarring, **fibrosis**, and **atrophy** of the spleen, which would likely be present in this **adult patient**.

Asplenic patients are more susceptible to infections with encapsulated bacteria (eg, group B *Streptococcus*, *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Neisseria meningitidis*, *Salmonella typhi*).

(Choice A) Splenic congestion occurs during a splenic sequestration crisis (marked hemoglobin decrease, rapidly enlarging spleen), which develops due to vaso-occlusion within the cords of Billroth and splenic pooling of erythrocytes. However, repeated infarction leads to functional asplenia and autosplenectomy (splenic atrophy) by late childhood/adolescence.

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(Choice A) Splenic congestion occurs during a splenic sequestration crisis (marked hemoglobin decrease, rapidly enlarging spleen), which develops due to vaso-occlusion within the cords of Billroth and splenic pooling of erythrocytes. However, repeated infarction leads to functional asplenia and autosplenectomy (splenic atrophy) by late childhood/adolescence.

(Choices B and D) Splenic cyst formation typically occurs due to infection. Splenic infiltration can be seen with metastatic neoplasms but is not a feature of SCD.

(Choice E) The white pulp of the spleen is composed of lymphoid tissue. Lymphoid hyperplasia may represent infection or malignancy.

Educational objective:
Sickle cell disease is characterized by repeated splenic infarctions that ultimately result in splenic atrophy and fibrosis, a process that is typically complete by late childhood/adolescence. After autosplenectomy, patients are predisposed to infections with encapsulated bacterial organisms.

Pathology	Hematology & Oncology	Sickle cell
Subject	System	Topic

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Item 2 of 2

The patient is admitted to the hospital and receives opioid analgesics and intravenous fluids. He has no evidence of active infection. His hemoglobin electrophoresis results are consistent with sickle cell disease (hemoglobin SS). Further laboratory evaluation shows a mean corpuscular volume of 113 μm³ and a reticulocyte index of 1.5, which is low given the patient's severe anemia. Which of the following is the most likely cause of this patient's macrocytosis?

A. ~~Extramedullary erythropoiesis~~ (30%)
B. Increased folic acid requirement (54%)
C. Iron overload (2%)
D. Liver disease (5%)
E. ~~Myelodysplastic syndrome~~ (7%)

Incorrect
Correct answer

54%
Answered correctly

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This patient has **macrocytic** anemia (mean corpuscular volume [MCV] >100 μm³). Severe macrocytosis (**MCV >110 μm³**) is usually due to **megaloblastic anemia**, a subtype of macrocytic anemia caused by impaired DNA synthesis. Cytoplasmic components then accumulate within the slowly dividing erythrocytes, producing cells that are larger than normal (macrocytes).

Patients with **sickle cell disease** (SCD) or other hemolytic anemias have **increased folic acid requirements** due to increased erythrocyte turnover. As such, they are prone to developing relative folic acid deficiency and megaloblastic anemia.

(Choice A) Extramedullary erythropoiesis can occur in SCD and lead to an elevated reticulocyte count and MCV, as the reticulocytes produced are larger than those released by the bone marrow. However, this patient's low reticulocyte index (representing the reticulocyte percentage corrected for the degree of anemia) suggests an inadequate response to anemia and a lack of erythropoiesis.

(Choice C) Patients with SCD may receive multiple transfusions for treatment of severe or symptomatic anemia. Transfusion related iron overload can cause severe liver disease, but would be unlikely to produce an MCV >110 μm³.

(Choice D) Macrocytosis can occur in liver failure due to an increase in circulating phospholipids and

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an MCV >110 μm³.

(Choice D) Macrocytosis can occur in liver failure due to an increase in circulating phospholipids and cholesterol that adsorb onto erythrocytes, resulting in membrane expansion. However, liver-associated macrocytosis is generally mild (<110 μm³) and this patient does not have any findings to suggest advanced liver disease (eg, ascities/edema, bleeding).

(Choice E) A disease of the elderly, myelodysplastic syndrome can cause macrocytic anemia. In the setting of a young patient with SCD and hemolytic anemia, however, folic acid deficiency is much more likely.

Educational objective:

An MCV >110 μm³ is highly suggestive of megaloblastic anemia, such as that caused by folic acid or vitamin B_{12} deficiency. Patients with chronic hemolytic anemia have increased folic acid requirements due to increased erythrocyte turnover and are predisposed to developing macrocytosis.

Pathology	Hematology & Oncology	Sickle cell
Subject	System	Topic

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A 34-year-old obese man presents to your office complaining of fatigue, daytime sleepiness and occasional headaches. When you inquire about his sleeping habits, he reports that he sleeps in a separate room from his wife because she finds his snoring annoying. On physical examination, his blood pressure is 160/90 mmHg and his heart rate is 80/min. His abdomen is soft and non-tender, his liver span is 9 cm, and his spleen is not palpable. Laboratory findings are:

Hematocrit	57%
WBC count	9,000/mm^3
Platelets	190,000/mm^3

Decreased oxygen delivery to which of the following organs is responsible for his increased hematocrit?

A. Brain (9%)
B. Liver (2%)
C. Spleen (2%)

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Hematocrit	57%
WBC count	9,000/mm^3
Platelets	190,000/mm^3

Decreased oxygen delivery to which of the following organs is responsible for his increased hematocrit?

A. Brain (9%)
B. Liver (2%)
C. Spleen (2%)
D. Bone marrow (3%)
E. Lungs (7%)
✓ F. Kidneys (74%)

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This patient most likely has obstructive sleep apnea (OSA), a disease characterized by recurrent episodes of asphyxia during sleep, often up to 500 times per night. In patients with OSA, peritubular cells in the renal cortex sense hypoxia and respond by releasing erythropoietin into the bloodstream. (Deficient erythropoietin production is the reason why many patients with chronic kidney disease develop anemia.) Erythropoietin stimulates erythrocyte production by binding to erythropoietin receptors on erythrocyte precursors in the bone marrow. This response is responsible for the secondary polycythemia that occurs in patients with chronic hypoxia secondary to OSA, COPD, right-to-left shunts and high altitude.

(Choice A) Brain doesn't produce erythropoietin.

(Choice B) The liver is the major site of erythropoietin production in the fetus.

(Choice C) The spleen is the major site of destruction of aged or defective erythrocytes. The spleen and liver are potential sites of extramedullary hematopoiesis.

(Choice D) Erythropoietin released by the kidneys circulates to the bone marrow where it stimulates erythroid progenitor cells to synthesize more erythrocytes.

(Choice E) Lung stretch receptors sense distention of the lungs. Stimulation of these receptors decreases

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(Choice D) Erythropoietin released by the kidneys circulates to the bone marrow where it stimulates erythroid progenitor cells to synthesize more erythrocytes.

(Choice E) Lung stretch receptors sense distention of the lungs. Stimulation of these receptors decreases the respiratory rate.

Educational Objective:
Renal cortical cells sense hypoxia and respond by synthesizing and releasing erythropoietin. Erythropoietin stimulates the production of erythrocytes in the bone marrow.

Pathology	Hematology & Oncology	Polycythemia
Subject	System	Topic

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A 4-year-old male dies in the hospital from overwhelming infection. Autopsy findings include bone deformities and hepatosplenomegaly. Clumps of erythroid precursor cells are found in the liver and the spleen. The presence of these precursor cells is most likely related to which of the following conditions?

- A. Frequent transfusions (7%)
- B. Immune deficiency (11%)
- C. Erythropoietin deficiency (8%)
- ✓ D. Chronic hemolysis (66%)
- E. Iron deficiency (2%)
- F. Cyanocobalamin deficiency (2%)
- G. Portal hypertension (0%)

Correct

66% Answered correctly

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The presence of erythroid precursor cells in the liver and spleen is indicative of extramedullary hematopoiesis, a condition characterized by erythropoietin-stimulated, hyperplastic marrow cell invasion of extramedullary organs. Extramedullary hematopoiesis is most frequently caused by severe chronic hemolytic anemias, such as β-thalassemia (which the child depicted here may well have had).

Extramedullary hematopoiesis can cause a range of skeletal abnormalities. The expanding mass of progenitor cells in the bone marrow thins the bony cortex and impairs bone growth. Pathologic fractures are common in the most symptomatic of children. Maxillary overgrowth and frontal bossing are associated with the characteristic "chipmunk facies" observed in the pediatric population.

(Choice A) Red blood cell transfusions limit extramedullary hematopoiesis by reducing hypoxia.

(Choice B) Immune deficiencies are not frequently associated with red blood cell hemolysis.

(Choice C) Erythropoietin deficiency is observed in patients with chronic renal disease and would be associated with anemia, not extramedullary hematopoiesis.

(Choice E) Iron deficiency results in a relative depression of erythropoietic activity and is not associated with extramedullary hematopoiesis.

(Choice F) Cyanocobalamin (vitamin B_{12}) deficiency causes a megaloblastic anemia that is not associated

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(Choice B) Immune deficiencies are not frequently associated with red blood cell hemolysis.

(Choice C) Erythropoietin deficiency is observed in patients with chronic renal disease and would be associated with anemia, not extramedullary hematopoiesis.

(Choice E) Iron deficiency results in a relative depression of erythropoietic activity and is not associated with extramedullary hematopoiesis.

(Choice F) Cyanocobalamin (vitamin B_{12}) deficiency causes a megaloblastic anemia that is not associated with extramedullary hematopoiesis.

(Choice G) Intrahepatic extramedullary hematopoiesis can cause portal hypertension, and portal hypertension can cause hepatosplenomegaly. The reverse is not true, however.

Educational Objective:
The presence of erythroid precursors in organs such as the liver and spleen is indicative of extramedullary hematopoiesis, a condition characterized by erythropoietin-stimulated, hyperplastic marrow cell invasion of extramedullary organs. Extramedullary hematopoiesis is most frequently caused by severe chronic hemolytic anemias, such as β-thalassemia.

Pathology Hematology & Oncology Hemolytic anemia

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A 34-year-old male who is being treated for acute leukemia develops oliguria. His serum creatinine level is 2.7 mg/dL. Renal biopsy reveals multiple uric acid crystals obstructing renal tubular lumen. The principal site of uric acid precipitation would be which of the following?

A. Proximal tubules due to high solute concentration (25%)

B. Proximal tubules due to impaired uric acid transport (19%)

C. ~~Loop of Henle due to urine hyposmolarity~~ (6%)

D. ~~Distal tubules due to high urine flow rate~~ (3%)

✓ E. Collecting ducts due to low urine pH (44%)

Correct

44%
Answered correctly

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Explanation

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Tumor lysis syndrome is an oncologic emergency. It often develops during chemotherapy for high-grade lymphomas, leukemias, and other tumors that have rapid cell turnover and high sensitivity to chemotherapy. When a large number of tumor cells are destroyed during chemotherapy, intracellular ions, such as potassium, phosphorous, and uric acid (a metabolite of tumor nucleic acid), are released into the serum and are then filtered by the kidneys.

Uric acid (pKa = 5.4) is soluble at physiologic pH, but precipitates in an acidic environment. The lowest pH along the nephron is found in the distal tubules and collecting ducts; so these are the segments of the nephron that become obstructed by uric acid crystals. Obstructive uropathy and acute renal failure follow.

The risk of tumor lysis syndrome can be reduced by urine alkalinization and hydration. Additionally, allopurinol (a xanthine oxidase inhibitor) is used to reduce uric acid production during the breakdown of tumor cells.

(Choice D) Ignore the anatomy portion of choice D and evaluate the latter portion. A "high urine flow rate" would universally decrease uric acid crystallization and precipitation. Therefore, this cannot possibly be the correct answer.

(Choices A, B and C) Uric acid does not precipitate in proximal tubules or in Henle's loop.

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(Choices A, B and C) Uric acid does not precipitate in proximal tubules or in Henle's loop.

Educational Objective:

Tumor lysis syndrome occurs when tumors with a high cell turnover are treated with chemotherapy. The lysis of tumor cells causes intracellular ions, such as potassium and phosphorous, and uric acid (metabolite of tumor nucleic acid) to be released into serum. Uric acid is soluble at physiologic pH, but it can precipitate in the normally acidic environment of distal tubules and collecting ducts. The prevention of tumor lysis syndrome includes urine alkalinization and hydration, as high urine flow and high pH along the nephron prevents crystallization and precipitation of uric acid.

Pathophysiology	Hematology & Oncology	Tumor lysis syndrome
Subject	System	Topic

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Researchers are conducting a study to determine the effectiveness of a novel humanized monoclonal antibody in patients with metastatic colorectal cancer. This medication works by binding to the programmed cell death-1 receptor on T cells to block its ligands from binding. They find this therapy is most effective in patients with a high degree of microsatellite instability or defects in DNA mismatch repairs. Which of the following best explains the favorable drug effect in this subset of patients?

A. Higher expression of P-glycoprotein (15%)
B. Higher number of cancer neoantigens (34%)
C. Higher rate of *KRAS* mutations (18%)
D. Higher rate of *p53* mutations (26%)
E. More intense desmoplastic reaction (5%)

Correct

34%
Answered correctly

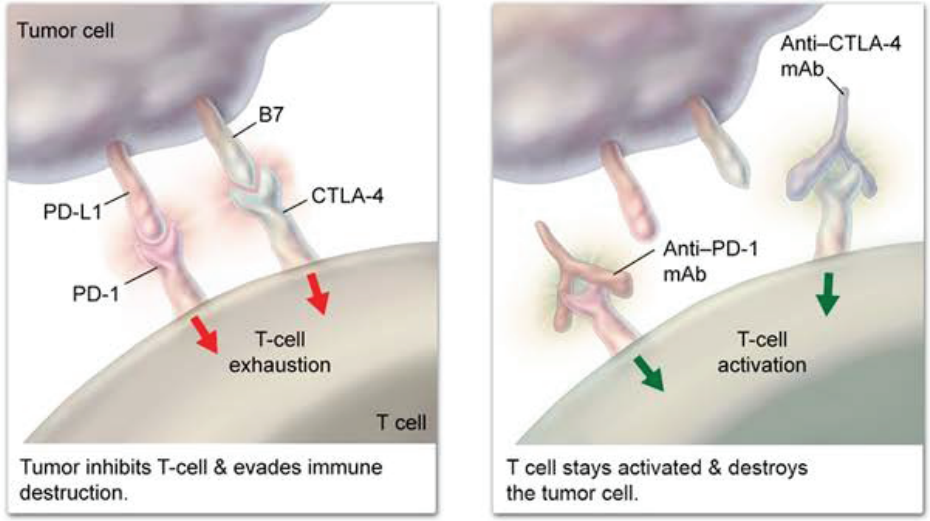
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Last Updated

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Cancer immunotherapy: anti–PD-1 & anti–CTLA-4 antibodies



CTLA-4 = cytotoxic T-lymphocyte–associated protein 4; **mAb** = monoclonal antibody; **PD-1** = programmed death receptor-1; **PD-L1** = programmed death ligand-1.

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Cancer cells that overexpress PD-L1 are less susceptible to cytotoxic T-cell–mediated destruction (enhanced T-cell exhaustion). These tumors can be treated with **monoclonal antibodies** that block the PD-1 receptor on T cells (eg, pembrolizumab, nivolumab) or the PD-1 ligand on cancer cells (eg, atezolizumab). Treatment stimulates the cytotoxic T-cell response; it is particularly effective against tumors with large quantities of neoantigens (eg, those with deficits in mismatch repair) because these tumors are particularly susceptible to recognition as "not-self."

(Choice A) P-glycoprotein is a multidrug transporter that can be used by cancer cells to pump cytotoxic chemotherapy out of the cell.

(Choice C) *KRAS* is a proto-oncogene that is part of the signaling pathway for the epidermal growth factor receptor. Activating mutations in *KRAS* lead to unregulated cellular growth. Tumors with activating mutations to *KRAS* are resistant to monoclonal antibodies against epidermal growth factor receptor because they have an activating mutation in a downstream signal.

(Choice D) p53 is a tumor-suppressor protein that inhibits cellular replication when DNA is damaged and induces apoptosis. Mutations to *p53* can lead to unregulated cellular growth and may inhibit cytotoxic chemotherapy–mediated cancer cell apoptosis.

(Choice E) Desmoplasia (dense fibrosis) around a tumor can reduce the ability of cytotoxic chemotherapy

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mutations to *KRAS* are resistant to monoclonal antibodies against epidermal growth factor receptor because they have an activating mutation in a downstream signal.

(Choice D) p53 is a tumor-suppressor protein that inhibits cellular replication when DNA is damaged and induces apoptosis. Mutations to *p53* can lead to unregulated cellular growth and may inhibit cytotoxic chemotherapy–mediated cancer cell apoptosis.

(Choice E) Desmoplasia (dense fibrosis) around a tumor can reduce the ability of cytotoxic chemotherapy to enter cancer cells.

Educational objective:

Cancer cells avoid immune recognition by overexpressing programmed death-ligand 1 (PD-L1), which binds to the programmed cell death-1 (PD-1) receptor on cytotoxic T cells and inhibits their response (T-cell exhaustion). Monoclonal antibodies that block PD-L1 and PD-1 are effective against cancers that express high levels of neoantigens on their surface because these tumors are particularly susceptible to immune recognition by cytotoxic T cells.

References

- PD-1 blockade in tumors with mismatch-repair deficiency.

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An 8-year-old boy is brought to the hospital due to severe headache and altered mental status. He is diagnosed with an aggressive, high-risk neuroblastoma. As part of his treatment, the patient will receive an autologous bone marrow transplant utilizing stem cells obtained from his peripheral blood. His pretransplant evaluation shows a history of a prior Epstein-Barr virus infection. This patient is at greatest risk for which of the following after transplantation?

A. Acute transplant rejection (4%)
B. Chronic transplant rejection (2%)
C. Graft versus host disease (9%)
D. New primary Epstein-Barr virus infection (10%)
E. Reactivation of Epstein-Barr virus (72%)

Correct

72%
Answered correctly

01 min, 18 secs
Time Spent

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Hematopoietic stem cell transplantation		
	Autologous	**Allogeneic**
Donor	Patient (self)	Related/unrelated (nonself)
Primary stem cell source	Peripheral blood	Bone marrow
Donor cell rejection	Uncommon	Possible, depending on match
Long-term immunosuppression	No	Yes
Graft versus host disease	No	Possible
Graft versus tumor activity	No	Possible
Infection transmission	No	Possible

Patients who undergo **hematologic stem cell transplantation** (HCT) first receive myeloablative chemotherapy, a highly cytotoxic regimen of medications that irreversibly kills existing hematopoietic stem cells. Once pancytopenia is established, they then receive an infusion of **donor hematopoietic stem**

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Infection transmission	No	Possible

Patients who undergo **hematologic stem cell transplantation** (HCT) first receive myeloablative chemotherapy, a highly cytotoxic regimen of medications that irreversibly kills existing hematopoietic stem cells. Once pancytopenia is established, they then receive an infusion of **donor hematopoietic stem cells**, which engraft in the bone marrow, proliferate, and subsequently reconstitute peripheral blood cells. Donor cells are classified as allogeneic when they are from a related or an unrelated donor and **autologous** when they are obtained **from the patient** (eg, pre-procedural peripheral blood or umbilical cord blood banked at birth).

With autologous transplantation, the human leukocyte antigens on MHC class I and II molecules will be a perfect match because the donor and recipient are the same individual; therefore, there is **no risk of graft rejection** (host cells attack the graft) or **graft versus host disease** (graft cells attack the host) because the delineation between self and nonself is preserved **(Choices A, B, and C)**.

Similarly, there is little risk of transfusing a new bloodborne infection (eg, HIV, hepatitis viruses, cytomegalovirus) because donor cells likely contain the same pathogens as the recipient **(Choice D)**. However, any chronic or latent infection **already present** in the donor may worsen or reactivate due to the **profound immunosuppression** caused by myeloablative chemotherapy in preparation for transplant.

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Similarly, there is little risk of transfusing a new bloodborne infection (eg, HIV, hepatitis viruses, cytomegalovirus) because donor cells likely contain the same pathogens as the recipient **(Choice D)**. However, any chronic or latent infection **already present** in the donor may worsen or reactivate due to the **profound immunosuppression** caused by myeloablative chemotherapy in preparation for transplant. Therefore, this patient who is infected with **Epstein-Barr virus** (EBV), an oncogenic human herpesvirus that establishes a **lifelong latent infection** in lymphocytes and epithelial cells, is at risk for **EBV reactivation** following transplantation.

Other common herpesviruses that may worsen after autologous transplant include cytomegalovirus, varicella zoster virus, and herpes simplex virus.

Educational objective:
Autologous hematologic stem cell transplantations reinfuse host cells from the peripheral blood or banked cord blood to reconstitute the bone marrow. Because the cells are genetically identical to the host, there is no risk of graft rejection or graft versus host disease. Although there is also no risk of transferring a new bloodborne pathogen, chronic or latent infections (eg, Epstein-Barr virus, cytomegalovirus, varicella zoster virus) may worsen due to immunosuppression following myeloablative chemotherapy.

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Autologous hematologic stem cell transplantations reinfuse host cells from the peripheral blood or banked cord blood to reconstitute the bone marrow. Because the cells are genetically identical to the host, there is no risk of graft rejection or graft versus host disease. Although there is also no risk of transferring a new bloodborne pathogen, chronic or latent infections (eg, Epstein-Barr virus, cytomegalovirus, varicella zoster virus) may worsen due to immunosuppression following myeloablative chemotherapy.

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A 63-year-old man comes to the emergency department due to abdominal pain. Physical examination shows abdominal tenderness without guarding or rebound. His laboratory test results are as follows:

Hemoglobin	8.9 g/dL
Platelets	134,000/mm^3
Total bilirubin	6.3 mg/dL
Lactate dehydrogenase	740 U/L
Haptoglobin	Low

On further investigation, magnetic resonance angiography of the abdomen reveals mesenteric vein thrombosis. Flow cytometry shows absence of CD55 on the surface of red blood cells. Which of the following is the most likely pathologic renal finding in this patient?

A. Cast nephropathy (22%)

B. Hemosiderosis (48%)

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Total bilirubin	6.3 mg/dL
Lactate dehydrogenase	740 U/L
Haptoglobin	Low

On further investigation, magnetic resonance angiography of the abdomen reveals mesenteric vein thrombosis. Flow cytometry shows absence of CD55 on the surface of red blood cells. Which of the following is the most likely pathologic renal finding in this patient?

- A. Cast nephropathy (22%)
- ✓ B. Hemosiderosis (48%)
- C. Interstitial nephritis (12%)
- D. Membranous glomerulonephritis (15%)
- E. Minimal change disease (1%)

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This patient's presentation is consistent with **paroxysmal nocturnal hemoglobinuria** (PNH), a disorder due to complement-mediated hemolysis. PNH is usually due to a mutated phosphatidylinositol glycan class A (***PIGA***) gene, which helps synthesize the glycosylphosphatidylinositol (**GPI**) anchor protein. This protein helps attach several **cell surface proteins** (eg, **CD55** decay accelerating factor, CD59 MAC inhibitory protein) that inactivate complement. Absence of these proteins leads to uncontrolled **complement-mediated hemolysis**.

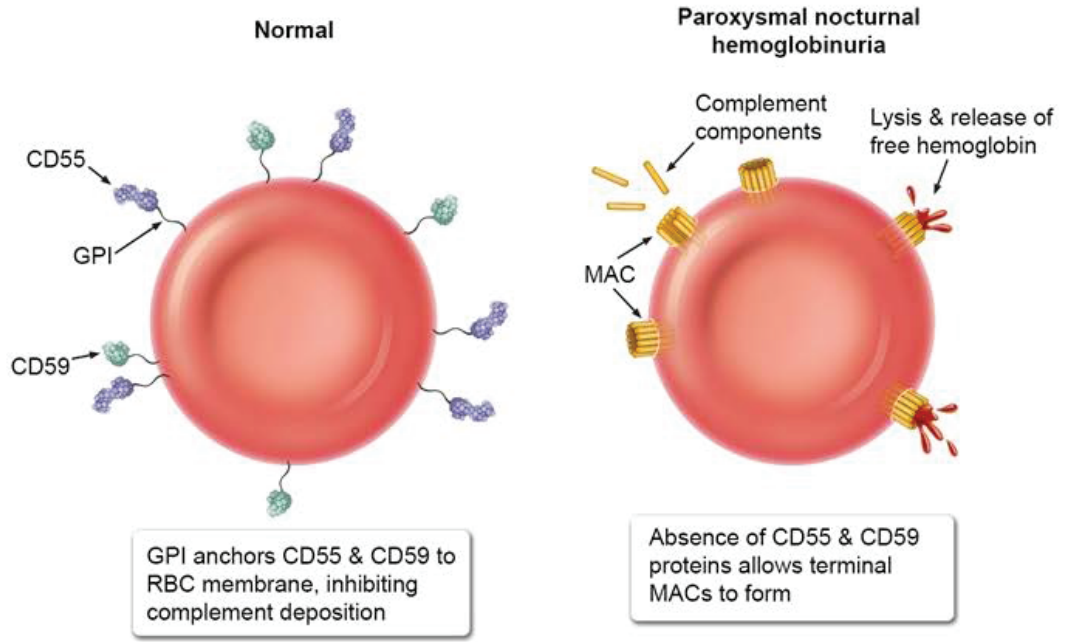
Manifestations of PNH include the following:

- Fatigue and jaundice due to **hemolytic anemia** (elevated bilirubin and lactate dehydrogenase, low haptoglobin, **hemoglobinuria** [which may be nocturnal])
- **Thrombosis** at atypical sites (eg, hepatic, portal, or cerebral veins) possibly due to the release of prothrombotic factors from lysed red blood cells and platelets (mesenteric vein thrombosis may explain this patient's abdominal pain)
- **Pancytopenia** due to stem cell injury

Chronic hemolysis with breakdown of iron-containing erythrocytes can also lead to **iron deposition** in the kidney (hemosiderosis), which can interfere with proximal tubule function and cause interstitial scarring and

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GPI = glycosylphosphatidyliositol; **MAC** = membrane attack complex; **RBC** = red blood cell.

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- **Pancytopenia** due to stem cell injury

Chronic hemolysis with breakdown of iron-containing erythrocytes can also lead to **iron deposition** in the kidney (hemosiderosis), which can interfere with proximal tubule function and cause interstitial scarring and cortical infarcts. The hemosiderosis combined with microvascular thrombosis can increase the risk of chronic kidney disease.

(Choices A and C) Cast nephropathy is usually seen in multiple myeloma and is due to large amounts of monoclonal free chain deposition in the kidney. Interstitial nephritis (inflammation in the area surrounding the renal tubules) is most commonly due to drugs (eg, analgesics, antibiotics), recent infection, or systemic conditions (eg, sarcoidosis).

(Choices D and E) Membranous glomerulonephritis can be associated with systemic lupus erythematosus, drugs (eg, nonsteroidal anti-inflammatory drugs [NSAIDs]), hepatitis B and C, or solid tumor malignancies (eg, lung, prostate, gastrointestinal). Minimal change disease can be associated with drugs (eg, NSAIDs), hematologic malignancies (eg, lymphoma, leukemia), or allergens (eg, fungi).

Educational objective:
Paroxysmal nocturnal hemoglobinuria is due to a gene defect that leads to uncontrolled complement-mediated hemolysis. The classic triad includes hemolytic anemia (hemoglobinuria), pancytopenia, and thrombosis at atypical sites. Chronic hemolysis can cause iron deposition in the kidney (hemosiderosis)

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Educational objective:
Paroxysmal nocturnal hemoglobinuria is due to a gene defect that leads to uncontrolled complement-mediated hemolysis. The classic triad includes hemolytic anemia (hemoglobinuria), pancytopenia, and thrombosis at atypical sites. Chronic hemolysis can cause iron deposition in the kidney (hemosiderosis).

References

- Paroxysmal nocturnal hemoglobinuria
- Fanconi syndrome and CKD in a patient with paroxysmal nocturnal hemoglobinuria and hemosiderosis.

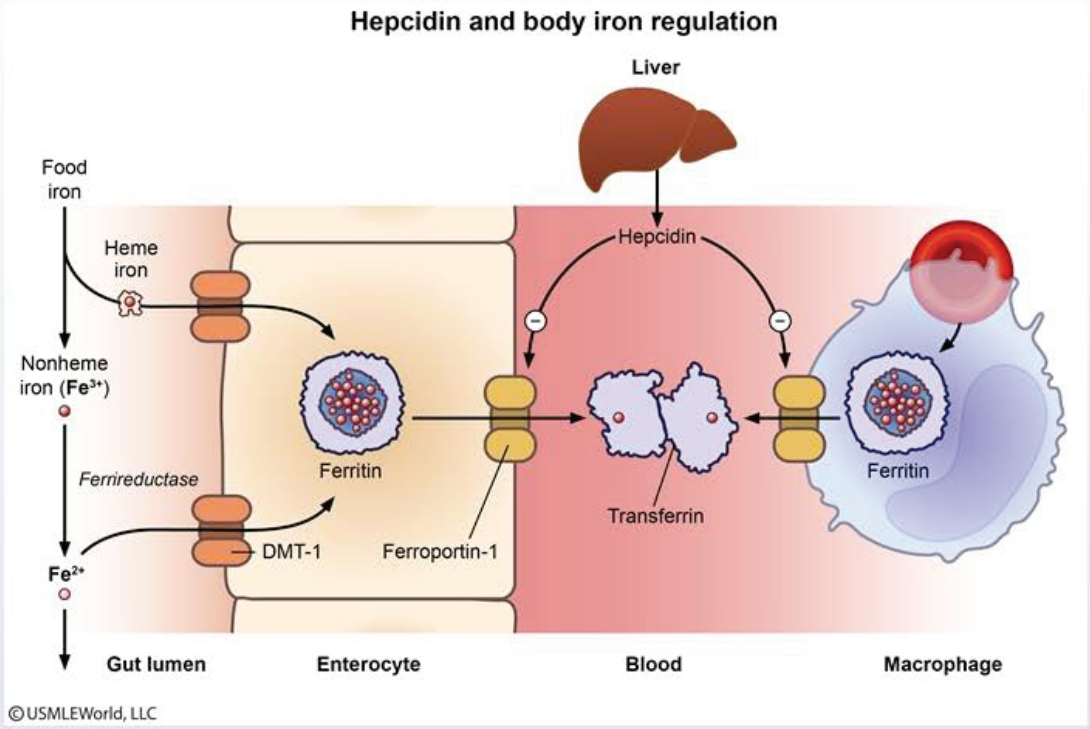
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A 41-year-old woman with a long history of menorrhagia comes to the physician due to a low hemoglobin level identified on routine laboratory evaluation. She is diagnosed with iron deficiency anemia and started on oral ferrous sulfate. After 3 months of therapy, her laboratory values have improved. She now asks about stopping her supplement as she is concerned about iron buildup and damage to vital organs. The physician reassures her and explains that iron homeostasis is maintained by multiple types of cells in the body. Which of the following cells secrete a substance that controls iron storage and release by other cells involved in iron homeostasis?

A. ~~Biliary lining cells~~ (0%)
B. ~~Bone marrow macrophages~~ (11%)
C. ~~Bone marrow stem cells~~ (1%)
D. Hepatic parenchymal cells (66%)
E. ~~Intestinal epithelial cells~~ (17%)
F. Renal tubular cells (2%)

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Hepcidin is an acute phase reactant synthesized by the liver that acts as the **central regulator of iron homeostasis**. High iron levels and inflammatory conditions increase the synthesis of hepcidin, while

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Hepcidin is an acute phase reactant synthesized by the liver that acts as the **central regulator of iron homeostasis**. High iron levels and inflammatory conditions increase the synthesis of hepcidin, while hypoxia and increased erythropoiesis act to lower hepcidin levels. Hepcidin influences body iron storage through its interaction with **ferroportin**, a transmembrane protein responsible for transferring intracellular iron to the circulation. Upon binding hepcidin, ferroportin is internalized and degraded, decreasing intestinal iron absorption and inhibiting the release of iron by macrophages.

Regulation of intestinal iron absorption is crucial for maintaining iron homeostasis, since blood loss is the only way of removing large amounts of iron from the body. Iron absorption from the proximal small intestine is facilitated by the divalent metal transporter-1 (DMT-1). Once inside the intestinal cells, iron may take 1 of 2 paths:

1. Iron may bind to ferritin (a primarily intracellular iron-binding protein) and remain stored within the enterocyte. The stored iron is excreted in the stool as enterocytes slough off and are replaced.
2. Iron may enter the circulation through ferroportin, the basolateral iron transporter of the enterocyte. Free iron released into the circulation is transported throughout the body by transferrin (an iron-binding transport protein), which becomes internalized after interacting with transferrin receptors present on all cells.

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cells.

(Choice A) Hepcidin is secreted primarily by hepatocytes; biliary cells produce only a limited amount of hepcidin that is mainly excreted in the bile.

(Choices B and C) When senescent red blood cells are destroyed by macrophages, the iron is recycled by the reticuloendothelial system for use in new erythroid precursors. Iron released by macrophages under the governance of hepcidin binds rapidly to transferrin and is delivered to the bone marrow, where erythroid precursors use it to synthesize hemoglobin. This internal iron cycle conserves the body's iron very efficiently, and only small amounts of additional iron are required for daily red cell production in the absence of significant blood loss.

(Choice E) Enterocytes store iron for excretion in the feces or transport it into the circulation depending on circulating levels of the polypeptide hormone hepcidin. Lower hepcidin levels favor iron absorption and accumulation in the body.

(Choice F) The renal tubular cells play a limited role in iron metabolism by secreting lactoferrin, which binds to free iron in the urine and possibly recovers it for metabolic use.

Educational objective:

Hepcidin is a polypeptide synthesized by the liver that acts as the central regulator of iron homeostasis

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Educational objective:

Hepcidin is a polypeptide synthesized by the liver that acts as the central regulator of iron homeostasis. High iron levels and inflammatory conditions increase the synthesis of hepcidin; hypoxia and increased erythropoiesis act to lower hepcidin levels. Low hepcidin levels increase intestinal iron absorption and stimulate iron release by macrophages.

References

- Regulation of cellular iron metabolism

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A 62-year-old woman comes to the office due to a painless neck mass that has gradually enlarged over several months. She also has had fatigue, night sweats, and unintentional weight loss. Physical examination shows rubbery, nontender, bilateral cervical lymphadenopathy. Imaging studies reveal mediastinal and abdominal lymphadenopathy, and subsequent excisional lymph node biopsy is consistent with diffuse large B cell lymphoma. The patient receives combination chemotherapy, which leads to rapid lysis of neoplastic cells. She also receives rasburicase prior to and during treatment. This medication helps to protect normal organs by which of the following mechanisms?

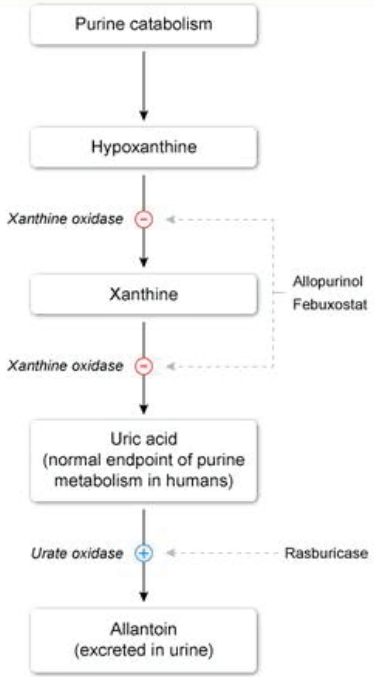
A. Converting uric acid into more soluble metabolites (78%)
B. ~~Forming insoluble complexes with phosphate~~ (1%)
C. Inhibiting uric acid formation after cell lysis (13%)
D. ~~Supplying a thiol group to inactivate toxic metabolites~~ (4%)
E. ~~Supplying necessary cofactors blocked by a chemotherapeutic agent~~ (1%)

78% 01 min, 32 secs 11/08/2020

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Tumor lysis syndrome (TLS) is an oncologic emergency that primarily develops during initial chemotherapy for high-grade lymphomas, leukemias, and other cancers with rapid cell turnover, substantial tumor burden, or high sensitivity to chemotherapy. When large numbers of tumor cells are destroyed in a short period, massive quantities of intracellular tumor products are released into the circulation, which frequently results in the following:

- Hyperkalemia, which can cause fatal heart arrhythmias.
- Hyperphosphatemia, which precipitates calcium in the renal tubules and collecting system, leading to systemic hypocalcemia and acute renal injury from calcium-phosphate stones.
- Hyperuricemia, which precipitates urate crystals in the renal tubules and collecting system, leading to acute renal injury.

Aggressive **intravenous fluids** during and after chemotherapy can help prevent kidney injury by flushing phosphorous and uric acid out of the kidneys. Treatment with an agent that reduces the formation of uric acid is also generally required to limit the formation of uric acid stones, including 1 of the following:

- **Rasburicase** is a recombinant version of **urate oxidase**, an enzyme present in many mammals, but not in humans. Urate oxidase converts uric acid into **allantoin**, a purine metabolite that is 5-10 times **more soluble** than uric acid and therefore far less likely to precipitate in the kidney.

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more soluble than uric acid and therefore far less likely to precipitate in the kidney.

- Allopurinol is a purine decoy that competitively inhibits xanthine oxidase (and other enzymes involved in purine metabolism), which reduces the conversion of purine metabolites into xanthine and uric acid **(Choice C)**. Febuxostat is a non-purine selective inhibitor of xanthine oxidase; it is similar to allopurinol, but it has fewer adverse effects and drug interactions.

(Choice B) Phosphate binders (eg, sevelamer) are used to manage hyperphosphatemia in patients with chronic kidney disease. Rasburicase does not target phosphate.

(Choice D) Mesna can prevent hemorrhagic cystitis in patients receiving cyclophosphamide or ifosfamide; it supplies a thiol group that inactivates the toxic metabolite (acrolein) of these chemotherapeutic agents.

(Choice E) Folinic acid (leucovorin) provides a reduced form of folic acid to counter the methotrexate-induced block in folic acid metabolism. It "rescues" gastrointestinal mucosa and bone marrow cells from the effects of methotrexate (which causes cell death in rapidly dividing cells).

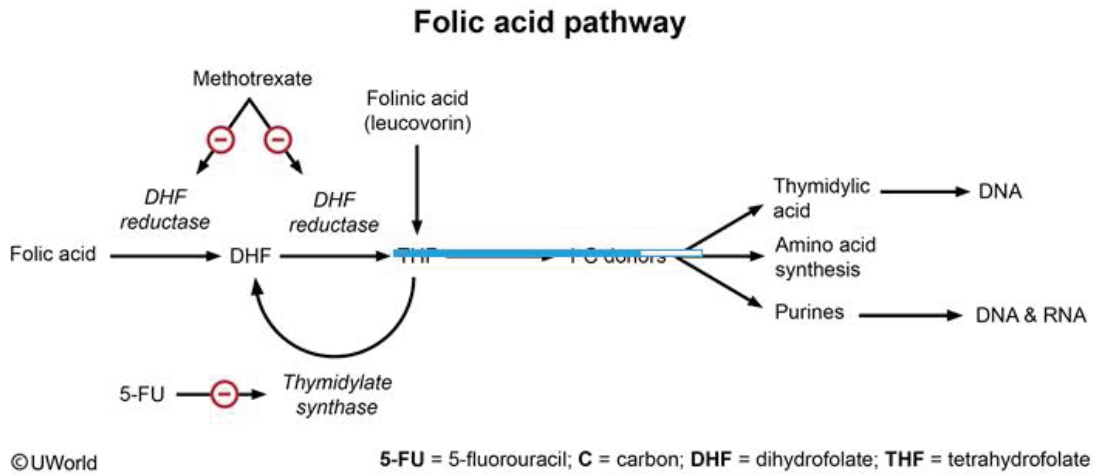
Educational objective:
Tumor lysis syndrome primarily develops during chemotherapy for cancers with rapid cell turnover, substantial tumor burden, or high sensitivity to chemotherapy. It is characterized by hyperphosphatemia, hypocalcemia, hyperkalemia, and hyperuricemia. Prevention involves intravenous fluids to flush the

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Educational objective:

Tumor lysis syndrome primarily develops during chemotherapy for cancers with rapid cell turnover, substantial tumor burden, or high sensitivity to chemotherapy. It is characterized by hyperphosphatemia, hypocalcemia, hyperkalemia, and hyperuricemia. Prevention involves intravenous fluids to flush the kidneys and the use of hypouricemic agents (eg, rasburicase, allopurinol, febuxostat).

References

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A 10-year-old boy comes to the office for a first visit. His family recently came to the United States as political refugees. The patient's mother says that he has required several blood product transfusions due to anemia, but she does not have prior records available with her. On examination, the patient's temperature is 37.1 C (98.8 F). BMI is 21 kg/m^2. Examination is notable for conjunctival pallor and moderate splenomegaly. Laboratory results are as follows:

Hemoglobin	9.4 g/dL
Platelets	240,000/mm^3

Enzyme assays performed on circulating blood cells demonstrate low pyruvate kinase activity. Which of the following is the most likely cause of this patient's splenomegaly?

A. Inflammatory infiltration (1%)
B. Myeloproliferative disorder (5%)
C. Passive splenic congestion (27%)
D. Presence of circulating immune complexes (4%)

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A. Inflammatory infiltration (1%)
B. Myeloproliferative disorder (5%)
C. Passive splenic congestion (27%)
D. Presence of circulating immune complexes (4%)
E. Red pulp hyperplasia (35%)
F. Undegraded metabolite accumulation (25%)

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Pyruvate kinase is a glycolytic pathway enzyme that converts phosphoenolpyruvate to pyruvate, resulting in the generation of a molecule of **ATP**. Allosteric stimulation of pyruvate kinase (by fructose 1,6-bisphosphate) stimulates glycolysis. Mature red blood cells (RBCs), which do not contain mitochondria, rely on lactate as the main metabolite for glycolysis.

Most of the ATP produced is used for transport of cations against a concentration gradient in the RBC membrane. Therefore, pyruvate kinase deficiency, which results in insufficient ATP production, disrupts this gradient, leading to water and potassium loss, defective maintenance of membrane architecture (echinocyte formation), and **hemolysis**. As reticuloendothelial cells in the splenic **red pulp** are involved in removal of damaged RBCs, their increased activity in the setting of pyruvate kinase deficiency causes them to undergo hyperplasia, resulting in **splenomegaly**.

(Choice A) The spleen is important in fighting infectious pathogens in the body; therefore, many acute and chronic infections lead to enlargement of the spleen due to proliferation of lymphoid tissue.

(Choice B) Disorders such as leukemia and lymphoma result in splenomegaly from neoplastic proliferation of lymphoid tissue within the spleen.

(Choice C) Passive congestion of the spleen with blood occurs in the setting of portal hypertension, splenic vein thrombosis, or congestive heart failure. Resultant splenic sinusoid dilation can lead to

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(Choice B) Disorders such as leukemia and lymphoma result in splenomegaly from neoplastic proliferation of lymphoid tissue within the spleen.

(Choice C) Passive congestion of the spleen with blood occurs in the setting of portal hypertension, splenic vein thrombosis, or congestive heart failure. Resultant splenic sinusoid dilation can lead to splenomegaly.

(Choice D) In infective endocarditis, circulating immune complexes can deposit in the kidneys and the spleen, likely contributing to splenomegaly.

(Choice F) Splenomegaly in the lysosomal storage diseases Niemann-Pick disease and Gaucher disease is due to the accumulation of sphingomyelin and glucocerebrosides, respectively.

Educational objective:
Pyruvate kinase deficiency causes hemolytic anemia due to failure of glycolysis and resultant failure to generate sufficient ATP to maintain erythrocyte structure. In this case, splenic hyperplasia results from increased work of the splenic parenchyma, which must remove these deformed erythrocytes from the circulation.

Pathology Hematology & Oncology Hemolytic anemia

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A 32-year-old woman comes to the office due to several days of fatigue and malaise. She has no significant medical history and has had no recent sick contacts. The patient does not appear to be in acute distress. Evaluation reveals severe thrombocytopenia. Thrombotic thrombocytopenic purpura is suspected. Which of the following findings is required to make the diagnosis?

A. Abnormal neurologic examination (15%)
B. Elevated liver aminotransferases (3%)
C. Fever (6%)
✓ D. Hemolytic anemia (52%)
E. Positive Coombs testing (18%)
F. Renal failure (4%)

Correct

52%
Answered correctly

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Last Updated

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Thrombotic thrombocytopenic purpura	
Pathophysiology	• ↓ ADAMTS-13 level → uncleaved vWF multimers → platelet trapping & activation • Acquired (autoantibody) or hereditary
Clinical features	• Hemolytic anemia (↑ LDH, ↓ haptoglobin) with schistocytes on peripheral smear • Thrombocytopenia (↑ bleeding time, normal PT/PTT) • Sometimes with: ◦ Renal failure ◦ Neurologic manifestations ◦ Fever

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Thrombotic thrombocytopenic purpura (TTP) is a **thrombotic microangiopathy** characterized by the formation of platelet-rich thrombi in the microvasculature. It is caused by severe deficiency of **ADAMTS13**, an enzyme that cleaves ultra-large von Willebrand factor multimers on the endothelial surface. Loss of ADAMTS13 triggers spontaneous platelet aggregation and activation, which results in **thrombocytopenia** due to platelet consumption and **microangiopathic hemolytic anemia** (MAHA) due to mechanical shearing of passing red blood cells.

Acquired TTP (autoantibody against ADAMTS13) was initially described as a pentad of fever, neurologic symptoms, kidney disease, MAHA, and thrombocytopenia. However, up to one-third of patients do not have neurologic abnormalities, half have normal kidney function, and only one-fifth have fever **(Choices A, C, and F)**. In fact, many with acquired TTP have minimal signs of toxicity (as in this case). Therefore, the only factors required for further evaluation of suspected thrombotic microangiopathy (eg, TTP, HUS) are the presence of **thrombocytopenia and MAHA** on peripheral blood smear (eg, **schistocytes**); significantly reduced ADAMTS13 activity can help confirm a specific diagnosis of TTP.

Plasma exchange is life-saving and should be considered in patients who have MAHA and thrombocytopenia and in whom TTP is suspected (untreated patients have a mortality rate of up to 90%).

(Choice B) Liver aminotransferases can sometimes be elevated in hemolytic anemia because these enzymes are present in erythrocytes. However, in this case, elevated aminotransferases are a nonspecific

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reduced ADAMTS13 activity can help confirm a specific diagnosis of TTP.

Plasma exchange is life-saving and should be considered in patients who have MAHA and thrombocytopenia and in whom TTP is suspected (untreated patients have a mortality rate of up to 90%).

(Choice B) Liver aminotransferases can sometimes be elevated in hemolytic anemia because these enzymes are present in erythrocytes. However, in this case, elevated aminotransferases are a nonspecific finding that would not be useful for confirming the presence of a thrombotic microangiopathy such as TTP.

(Choice E) Coombs testing evaluates for the presence of immunoglobulin on the erythrocyte surface. In TTP, the hemolytic anemia is triggered by red blood cell shearing in the microvasculature, not immunoglobulin attachment; therefore, Coombs testing would be unrevealing.

Educational objective:
Thrombotic thrombocytopenic purpura is a thrombotic microangiopathy resulting in microangiopathic hemolytic anemia and thrombocytopenia, findings that are essential for making the diagnosis. It is triggered by severe deficiency in ADAMTS13 levels.

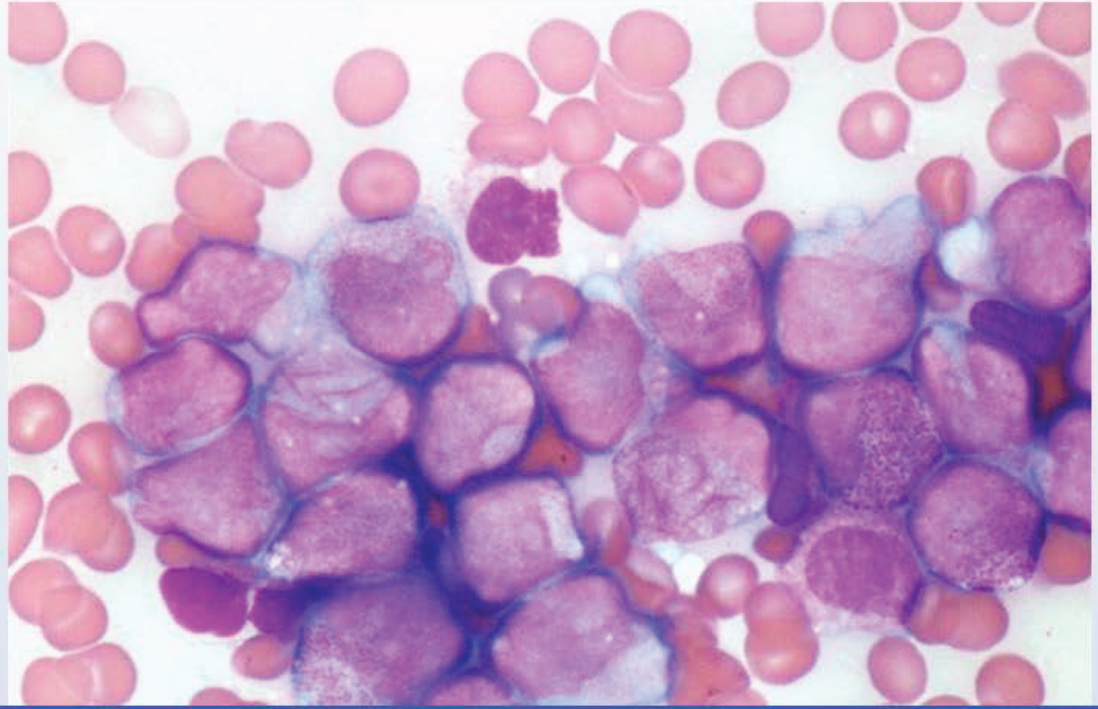
References

- How I treat thrombotic thrombocytopenic purpura and atypical haemolytic uraemic syndrome.
- Management of thrombotic thrombocytopenic purpura: current perspectives

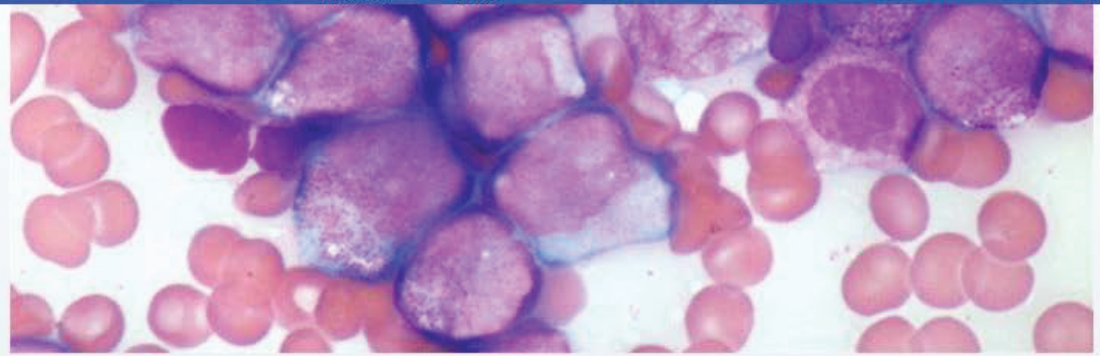
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A 36-year-old man presents to your office with persistent fever, bleeding gums, and a sore throat. Peripheral blood microscopy findings are shown in the image below.



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These cells contain structures that would stain positive for which of the following?

A. Major basic protein (7%)

B. Myeloperoxidase (64%)

C. Platelet-derived growth factor (4%)

D. Tartrate resistant acid phosphatase (10%)

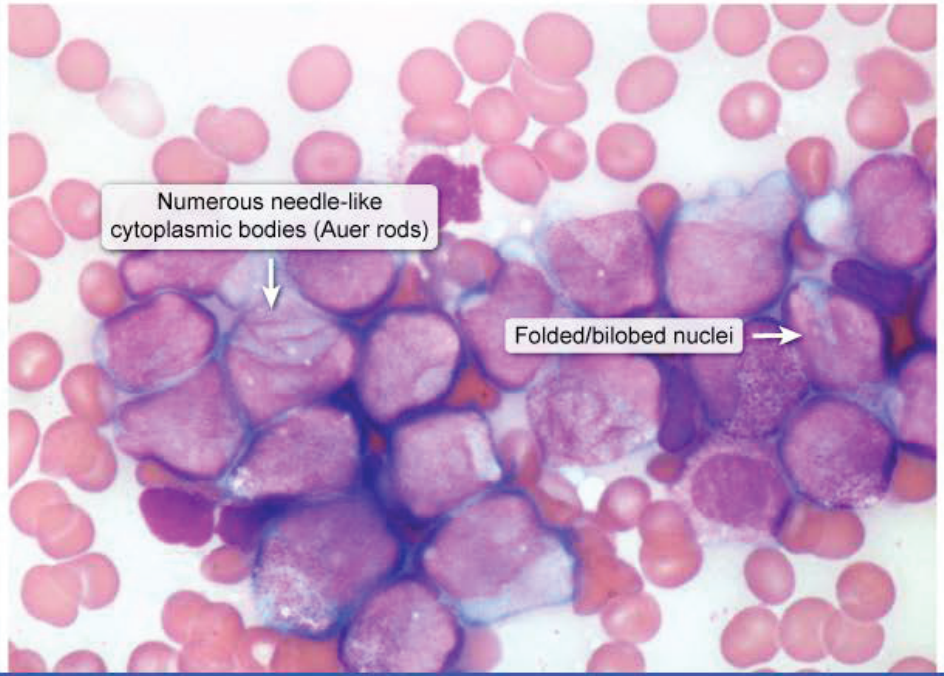
E. Terminal deoxynucleotidyl transferase (13%)

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Explanation

Acute promyelocytic leukemia



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This peripheral blood smear shows **myeloblasts**, which are large myelogenous cells with abundant basophilic cytoplasm and large nuclei that can be folded or bilobed. Myeloblasts often have a number of coarse rod/needle-shaped intracytoplasmic granules (eg, **Auer rods**) that stain positive for **myeloperoxidase**. Auer rods indicate myeloid differentiation.

Acute promyelogenous leukemia (APL) is a variant of acute myelogenous leukemia (AML), in which immature cells of myeloid origin are unable to differentiate and mature. They proliferate in the bone marrow and suppress the growth and multiplication of other hematopoietic precursors. The clinical manifestations of APL, such as anemia (fatigue, pallor), **thrombocytopenia** (petechiae, hemorrhages), and **neutropenia** (fever, opportunistic infections), result from marrow replacement by leukemic cells.

(Choice A) Major basic protein is found in eosinophil granules and helps to defend against parasites.

(Choice C) Platelet-derived growth factor receptor mutations play a role in gastrointestinal stromal tumors.

(Choice D) Hairy cell leukemia stains positively for tartrate resistant acid phosphatase (TRAP). The neoplastic cells are B lymphocyte precursors and are $CD20^{+}$. Hairy cell leukemia presents with splenomegaly, fatigue and pancytopenia.

(Choice E) Terminal deoxynucleotidyl transferase (TdT) is responsible for adding nucleotides to the V, D and J regions of the antibody gene for antibody diversity. It is a marker of immature lymphocytes, both B

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neutropenia (fever, opportunistic infections), result from marrow replacement by leukemic cells.

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(Choice D) Hairy cell leukemia stains positively for tartrate resistant acid phosphatase (TRAP). The neoplastic cells are B lymphocyte precursors and are $CD20^{+}$. Hairy cell leukemia presents with splenomegaly, fatigue and pancytopenia.

(Choice E) Terminal deoxynucleotidyl transferase (TdT) is responsible for adding nucleotides to the V, D and J regions of the antibody gene for antibody diversity. It is a marker of immature lymphocytes, both B and T cells. Neoplastic cells in acute lymphoblastic leukemia (ALL) are TdT positive. ALL mainly affects children.

Educational Objective:
Auer rods are deformed azurophilic granules found in the cytoplasm of myeloblasts that stain positively for myeloperoxidase. Auer rods are found in abundance in AML M3 (acute promyelocytic leukemia).

Pathology	Hematology & Oncology	Acute myeloid leukemia
Subject	System	Topic

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A 5-year-old boy is brought to the office by his parents who say that he "looks yellow" and has been uncharacteristically tired lately. He has had upper respiratory tract infection symptoms for the past 3 days, including cough, rhinorrhea, sneezing, and sore throat. The parents say that "a lot of kids at daycare have been sick lately." The patient has no prior medical problems. He is consistently at the 50th percentile for height and weight. He takes no medications, and his immunizations are up to date. Pallor, scleral icterus, and palpable splenomegaly are seen on examination. Laboratory results are as follows:

Complete blood count	
Hemoglobin	9 g/dL
Reticulocytes	10.8%
Platelets	218,000/mm^3
Leukocytes	7500/mm^3
Liver studies	
Total bilirubin	3 mg/dL

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Leukocytes	7500/mm^3
Liver studies	
Total bilirubin	3 mg/dL
Direct bilirubin	0.8 mg/dL
Alkaline phosphatase	95 U/L
Aspartate aminotransferase (AST)	18 U/L
Alanine aminotransferase (ALT)	15 U/L

The patient recovers spontaneously after a few weeks. Peripheral smear of the boy's blood after recovery is shown in the exhibit. Which of the following is the most likely cause of this patient's condition?

A. Glucose-6-phosphate dehydrogenase enzyme deficiency (20%)

B. Imbalance between alpha and beta globin chain production (5%)

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Alkaline phosphatase	95 U/L
Aspartate aminotransferase (AST)	18 U/L
Alanine aminotransferase (ALT)	15 U/L

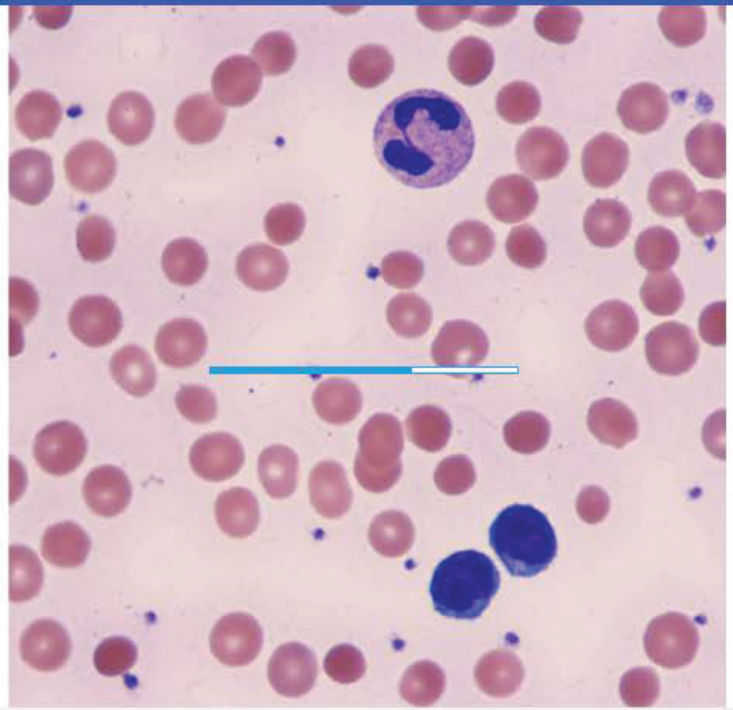
The patient recovers spontaneously after a few weeks. Peripheral smear of the boy's blood after recovery is shown in the exhibit. Which of the following is the most likely cause of this patient's condition?

A. Glucose-6-phosphate dehydrogenase enzyme deficiency (20%)
B. Imbalance between alpha and beta globin chain production (5%)
C. Nuclear maturation defect due to defective DNA synthesis (5%)
D. Polymerization of hemoglobin within red blood cells (5%)
E. Red blood cell membrane cytoskeleton abnormalities (63%)

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Alkaline phosphatase 95 U/L

Exhibit Display



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Hereditary spherocytosis	
Epidemiology	• Autosomal dominant inheritance (~75%) • Northern European descent
Clinical presentation	• Hemolytic anemia • Jaundice • Splenomegaly
Laboratory findings	• ↑ **Mean corpuscular hemoglobin concentration** • **Spherocytes** on peripheral smear • Negative Coombs test • ↑ Osmotic fragility on **acidified glycerol lysis test**
Treatment	• Splenectomy
Complications	• Pigmented gallstones • Aplastic crises from parvovirus B19 infection

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This patient's peripheral smear shows spherocytes, which are approximately two-thirds of the diameter of normal RBCs, more densely hemoglobinized at the periphery, and often lack a zone of central pallor. This

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This patient's peripheral smear shows spherocytes, which are approximately two-thirds of the diameter of normal RBCs, more densely hemoglobinized at the periphery, and often lack a zone of central pallor. This patient's presentation is consistent with hereditary spherocytosis (HS), an autosomal dominant hemolytic anemia due to a **red blood cell (RBC) membrane defect**. The mutation in HS most often affects the plasma-membrane scaffolding proteins **spectrin** and **ankyrin**. Without this scaffolding, spherocytes are less deformable than normal RBCs and are prone to sequestration and subsequent accelerated **destruction in the spleen**.

Clinical manifestations include **hemolytic anemia, jaundice** (increased RBC destruction results in greater bilirubin production), and **splenomegaly** (spherocytes have difficulty passing through the cords of Billroth and accumulate in the spleen). Infections can trigger hemolysis and lead to an acute hemolytic crisis, as seen in this patient. Age of diagnosis varies considerably, but many patients have jaundice and fatigue in times of increased hemolysis in the setting of viral infections.

(Choice A) Glucose-6-phosphate dehydrogenase (G6PD) enzyme deficiency anemia usually follows oxidative stress. Common triggers include drugs (sulfonamide or antimalarial agents), fava beans, and infections (viral hepatitis, pneumonia, or typhoid). Peripheral smears of G6PD deficiency anemia show bite

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oxidative stress. Common triggers include drugs (sulfonamide or antimalarial agents), fava beans, and infections (viral hepatitis, pneumonia, or typhoid). Peripheral smears of G6PD deficiency anemia show bite cells and Heinz bodies, not spherocytes.

(Choice B) An imbalance between alpha globin and beta globin chain production results in thalassemia. In this patient, the peripheral smear has no morphologic variants associated with thalassemia, such as target cells or hypochromic microcytes.

(Choice C) A nuclear maturation defect due to defective DNA synthesis is the pathophysiologic mechanism of megaloblastic anemia, which is most commonly caused by vitamin B_{12} and folic acid deficiencies. In this patient's peripheral smear, small spherocytes are primarily seen and not the enlarged oval cells and hypersegmented neutrophils of megaloblastic anemia.

(Choice D) Polymerization of hemoglobin occurs in sickle cell anemia. A missense mutation in the beta globin chain leads to the production of hemoglobin S, which has the capacity to polymerize in deoxygenated states. This polymerization leads to red blood cell membrane injury and deformation to a "sickle" shape seen on peripheral smear.

Educational objective:

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(Choice B) An imbalance between alpha globin and beta globin chain production results in thalassemia. In this patient, the peripheral smear has no morphologic variants associated with thalassemia, such as target cells or hypochromic microcytes.

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Educational objective:

Hereditary spherocytosis results from red cell cytoskeleton abnormalities, most commonly spectrin and ankyrin. Hemolytic anemia, jaundice, and splenomegaly are classic manifestations. Spherocytes are seen on peripheral blood smear.

References

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A 20-year-old man comes to the emergency department due to a 2-day history of increasing tiredness and exertional dyspnea. He also reports yellowish discoloration of the eyes and dark urine. The patient has no chronic medical conditions, but 5 days ago, he went to an urgent care clinic due to right leg cellulitis; a 7-day course of trimethoprim-sulfamethoxazole was prescribed. The cellulitis has improved. The patient, an exchange student from Israel, does not use tobacco, alcohol, or illicit drugs. Temperature is 37 C (98.6 F), blood pressure is 116/76 mm Hg, and pulse is 104/min. Physical examination shows mild scleral icterus, pale oral mucous membranes, a faint systolic ejection murmur, and a nontender abdomen with no organomegaly. Hemoglobin is 7.4 g/dL and mean corpuscular volume is 90 μm³. Which of the following additional findings are most likely present in this patient?

	Reticulocyte count	Lactate dehydrogenase	Haptoglobin	
A.	~~Decreased~~	~~Decreased~~	~~Normal~~	(0%)
B.	~~Decreased~~	~~Normal~~	~~Normal~~	(2%)
✓ C.	Increased	Increased	Decreased	(86%)

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7-day course of trimethoprim-sulfamethoxazole was prescribed. The cellulitis has improved. The patient, an exchange student from Israel, does not use tobacco, alcohol, or illicit drugs. Temperature is 37 C (98.6 F), blood pressure is 116/76 mm Hg, and pulse is 104/min. Physical examination shows mild scleral icterus, pale oral mucous membranes, a faint systolic ejection murmur, and a nontender abdomen with no organomegaly. Hemoglobin is 7.4 g/dL and mean corpuscular volume is 90 μm^3. Which of the following additional findings are most likely present in this patient?

	Reticulocyte count	Lactate dehydrogenase	Haptoglobin	
A.	~~Decreased~~	~~Decreased~~	~~Normal~~	(0%)
B.	~~Decreased~~	~~Normal~~	~~Normal~~	(2%)
✓ C.	Increased	Increased	Decreased	(86%)
D.	~~Increased~~	~~Normal~~	~~Normal~~	(5%)
E.	Normal	Increased	Decreased	(5%)

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Explanation

Glucose-6-phosphate dehydrogenase deficiency	
Epidemiology	• Hemolytic anemia due to oxidative stress (infection, sulfa drugs, fava beans) • X-linked: Asian, African, or Middle Eastern descent
Manifestations	• Pallor & fatigue • Dark urine, jaundice & icterus • Abdominal/back pain
Laboratory findings	• Hemolysis: ↓ hemoglobin, ↓ haptoglobin, ↑ bilirubin & LDH, ↑ reticulocytes • Peripheral smear: bite cells & Heinz bodies • Negative Coombs test • ↓ G6PD activity level (may be normal during attack)
Management	• Remove or treat responsible agent/condition • Provide supportive care
G6PD = glucose-6-phosphate dehydrogenase; **LDH** = lactate dehydrogenase.	

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This patient has anemia and signs of hemolysis (eg, dark urine, scleral icterus) after taking a **sulfa drug** (ie, trimethoprim-sulfamethoxazole), findings consistent with **glucose-6-phosphate dehydrogenase (G6PD) deficiency**. G6PD is a red blood cell (RBC) enzyme that helps neutralize reactive oxygen species by producing NADPH. In the absence of G6PD, oxygen radicals accumulate during times of **oxidative stress** (eg, infection, sulfa drugs, fava bean ingestion), causing damage to RBCs and intravascular hemolysis.

Characteristic findings of **hemolysis** include the following:

- **Normocytic anemia**, which can cause dyspnea, pallor, fatigue, or flow murmur (systolic ejection murmur due to hyperdynamic circulation)
- **Increased** production of **reticulocytes** (immature RBCs) by the bone marrow in response to the drop in hemoglobin
- **Increased** breakdown products of RBCs, including **lactate dehydrogenase** (LDH) and hemoglobin (Increased urinary excretion of hemoglobin occurs with intravascular hemolysis and causes dark urine.)
- **Decreased haptoglobin** because it binds free circulating hemoglobin

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(Increased urinary excretion of hemoglobin occurs with intravascular hemolysis and causes dark urine.)

- **Decreased haptoglobin** because it binds free circulating hemoglobin
- Degradation of hemoglobin (heme → biliverdin → bilirubin), resulting in **elevated indirect bilirubin**, which manifests as jaundice and scleral icterus

G6PD deficiency can be differentiated from other hemolytic anemias by the presence of Heinz bodies (inclusions of denatured hemoglobin) and bite cells (caused by phagocytic removal of Heinz bodies) on peripheral smear. Low G6PD activity within RBCs is diagnostic; however, this test may be inaccurate during an acute episode due to increased reticulocytes. Management generally involves avoiding known hemolytic triggers.

Educational objective:
Glucose-6-phosphate dehydrogenase deficiency presents with signs of anemia (eg, fatigue, pallor) and hemolysis (eg, jaundice, dark urine) after oxidative stress (eg, sulfa drug). Hemolysis is associated with reticulocytosis, increased lactate dehydrogenase, decreased haptoglobin, and elevated indirect bilirubin.

References

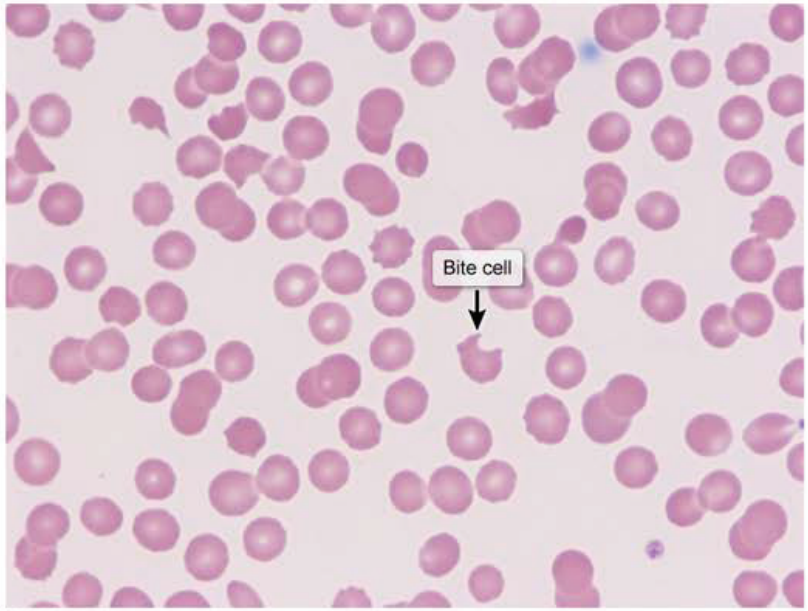
- Glucose-6-phosphate dehydrogenase deficiency.

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(Increased urinary excretion of hemoglobin occurs with intravascular hemolysis and causes dark

Exhibit Display

Glucose-6-phosphate dehydrogenase deficiency



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A 45-year-old man comes to the office due to a week of purulent nasal discharge, headache, sore throat, and nonproductive cough. He has no significant past medical history except for an episode of infectious mononucleosis at age 22. The patient smokes a pack of cigarettes daily. His temperature is 38 C (100.4 F). He has maxillary sinus tenderness, pharyngeal erythema, and tender anterior cervical lymphadenopathy. Laboratory results are as follows:

Leukocytes	58,000/mm^3
Neutrophils	42%
Myelocytes	30%
Metamyelocytes	8%
Band forms	1%
Blast cells	1%
Eosinophils	6%
Basophils	4%

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Metamyelocytes	8%
Band forms	1%
Blast cells	1%
Eosinophils	6%
Basophils	4%

The leukocyte alkaline phosphatase score is low. Which of the following is the most likely diagnosis?

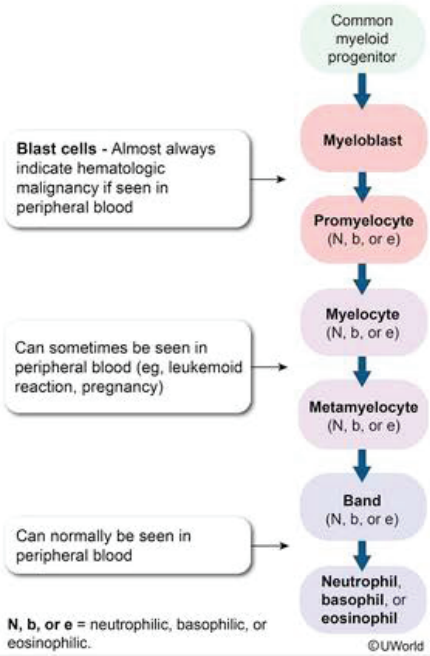
A. ~~Acute lymphoblastic leukemia~~ (1%)
B. Acute myelogenous leukemia (14%)
C. ~~Burkitt lymphoma~~ (13%)
D. ~~Chronic lymphocytic leukemia~~ (3%)
✓ E. Chronic myelogenous leukemia (44%)
✗ F. Diffuse large B-cell lymphoma (4%)

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Hematopoiesis: Myeloid lineage



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This patient with sinusitis is found to have a markedly elevated white blood cell (WBC) count with an increase in myeloid precursor forms on peripheral blood smear. The differential diagnosis is **chronic myelogenous leukemia** (CML) (uncontrolled mature granulocyte production, mostly neutrophils but also basophils and eosinophils) or leukemoid reaction (over-exuberant WBC response associated with bacterial infection or malignancy, among others). Both cause an **elevated WBC** count (≥50,000/mm^3) with **an increase in precursor forms** (eg, bands, metamyelocytes, myelocytes). However, the enzyme **leukocyte (neutrophil) alkaline phosphatase** is **decreased** in CML (as seen in this patient) because the WBCs are cytochemically abnormal; by contrast, it is normal or elevated in a leukemoid reaction **(Choice I)**.

Other clues to the diagnosis of CML are the predominance of myelocytes compared to more mature forms such as metamyelocytes (**"myelocytic bulge"**) and the absolute **basophilia and eosinophilia**. CML is confirmed by demonstration of the Philadelphia chromosome (translocation between chromosomes 9 and 22) or the *BCR-ABL1* fusion gene or mRNA. Immature blast cells (eg, myeloblasts, promyelocytes) are typically <2%. Management generally includes a tyrosine kinase inhibitor.

(Choice A) This patient has an abnormality of myeloid (not lymphoid) cells and his smear shows only 1% blasts. In general, >25% bone marrow lymphoblasts are seen in acute lymphoblastic leukemia, which is much more common in young children.

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(Choice B) Acute myelogenous leukemia is the most common acute leukemia in adults. However, the mean age at diagnosis is around 65, and most patients will have a WBC count of about 15,000-20,000/mm^3 with a significant increase in blast cells (eg, ≥20%) rather than the 1% seen in this patient.

(Choices C, F, and G) Follicular lymphoma, Burkitt lymphoma, and diffuse large B-cell lymphoma cause lymph node and/or soft-tissue (not peripheral blood) abnormalities. In addition, these cancers are all lymphoid, not myeloid, in nature.

(Choice D) Patients with chronic lymphocytic leukemia have increased circulating mature lymphoid cells, not increased myeloid cells.

(Choices H and J) Parasitic superinfection (which can lead to eosinophilia) and fungal infection would not explain the predominance of myeloid neutrophil precursor forms in this patient.

Educational objective:
Chronic myelogenous leukemia (CML) and leukemoid reaction can have presentations similar to leukocytosis; however, leukocyte (neutrophil) alkaline phosphatase level is normal or elevated in a leukemoid reaction but decreased in CML. The definitive diagnosis of CML requires demonstration of the Philadelphia chromosome t(9;22) or *BCR-ABL* fusion gene or mRNA.

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A 22-year-old man comes to the office due to recurrent blistering on the back of his hands and forearms for the past several years. The patient usually develops small itchy spots but lately has had large blisters that heal with hyperpigmentation after rupturing. He has used over-the-counter topical hydrocortisone and emollients, but the symptoms have not improved. The patient works as a night security guard and has had no exposure to chemicals or animals. He drinks 2-3 cans of beer daily. Physical examination shows vesicles and erosions on the dorsum of both hands. Which of the following enzymes is most likely deficient in this patient?

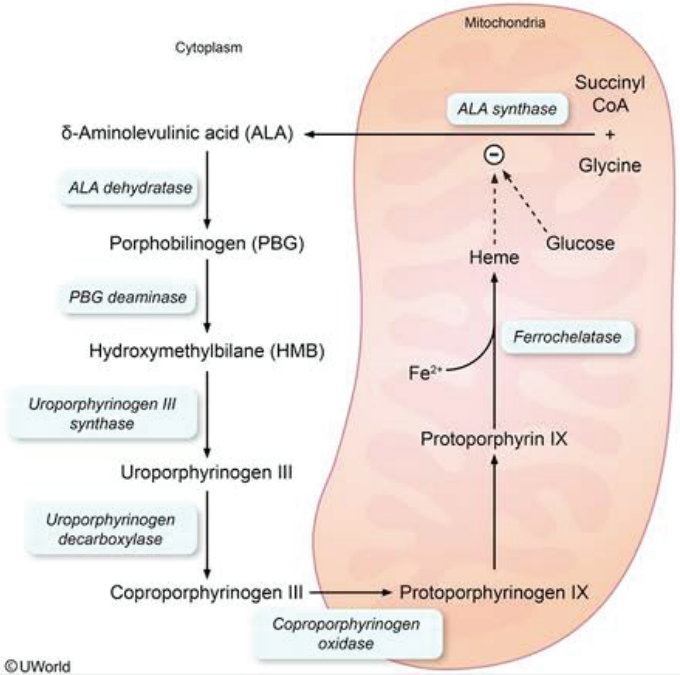
A. δ-Aminolevulinate dehydratase (7%)
B. δ-Aminolevulinate synthase (11%)
C. Bilirubin glucuronyl transferase (4%)
D. Porphobilinogen deaminase (22%)
E. Uroporphyrinogen decarboxylase (53%)

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Exhibit Display

Heme synthesis



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oxidase

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This patient most likely has **porphyria cutanea tarda (PCT)**, the most common disorder of porphyrin (eg, heme) synthesis. Enzyme deficiencies in the early steps in porphyrin synthesis cause abdominal pain and neuropsychiatric manifestations (due to metabolite buildup) without photosensitivity. **Late** step (ie, following porphobilinogen [PBG] conversion) derangements (eg, PCT) cause **photosensitivity**, which is thought to be due to the accumulation of **porphyrinogens** that react with oxygen on excitation by ultraviolet (sun) light.

PCT is caused by **uroporphyrinogen decarboxylase (UROD)** deficiency, which is either inherited or (more commonly) acquired, manifesting in the presence of iron and of susceptibility factors (eg, alcohol [as in this patient], smoking, halogenated hydrocarbons, hepatitis C, HIV). Photosensitivity presents as vesicle and **blister** formation on sun-exposed areas as well as edema, pruritus, pain, and erythema. Deficiencies in coproporphyrinogen oxidase, protoporphyrinogen oxidase, or ferrochelatase can also result in photosensitivity.

(Choices A and D) Deficiencies in aminolevulinate (ALA) dehydratase and PBG deaminase do not result in photosensitivity because the metabolites that accumulate are not porphyrinogens or porphyrins. PBG deaminase deficiency is seen with acute intermittent porphyria (classically presenting with abdominal pain

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oxidase

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(Choices A and D) Deficiencies in aminolevulinate (ALA) dehydratase and PBG deaminase do not result in photosensitivity because the metabolites that accumulate are not porphyrinogens or porphyrins. PBG deaminase deficiency is seen with acute intermittent porphyria (classically presenting with abdominal pain and neuropsychiatric manifestations).

(Choice B) Deficiency of ALA synthase will result in a decrease in formation of all porphyrins. This deficiency will not result in porphyria but will lead to a decrease in heme synthesis and concurrent hypochromic, microcytic anemia. Pyridoxal phosphate (vitamin B_6) is the cofactor required for activity of ALA synthase; therefore, pyridoxine deficiency can result in microcytic hypochromic anemia.

(Choice C) Bilirubin glucuronyl transferase is a hepatic enzyme responsible for the conjugation of bilirubin with glucuronide, improving solubility for biliary excretion. A decrease in glucuronyl transferase results in unconjugated hyperbilirubinemia.

Educational objective:
Enzyme deficiencies of the early steps in porphyrin synthesis cause neuropsychiatric manifestations without photosensitivity, whereas late step derangements lead to photosensitivity. Photosensitivity manifests as vesicle and blister formation on sun-exposed areas as well as edema, pruritus, pain, and erythema.

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A 13-year-old girl is undergoing hematologic evaluation. She is found to have a hemoglobin mutation that changes the partial pressure of oxygen at which hemoglobin is 50% saturated to 20 mm Hg. In comparison, normal hemoglobin becomes 50% saturated with oxygen at 26 mm Hg. Which of the following sequelae is this patient most likely to develop as a result of her mutation?

- A. Erythrocytosis (53%)
- B. Hypoxia-induced hemolysis (20%)
- C. ~~Increased erythrocyte osmotic fragility~~ (7%)
- D. ~~Megaloblastic erythrocyte changes~~ (2%)
- E. ~~Oxidant-induced hemolysis~~ (16%)

Incorrect
Correct answer
A

53%
Answered correctly

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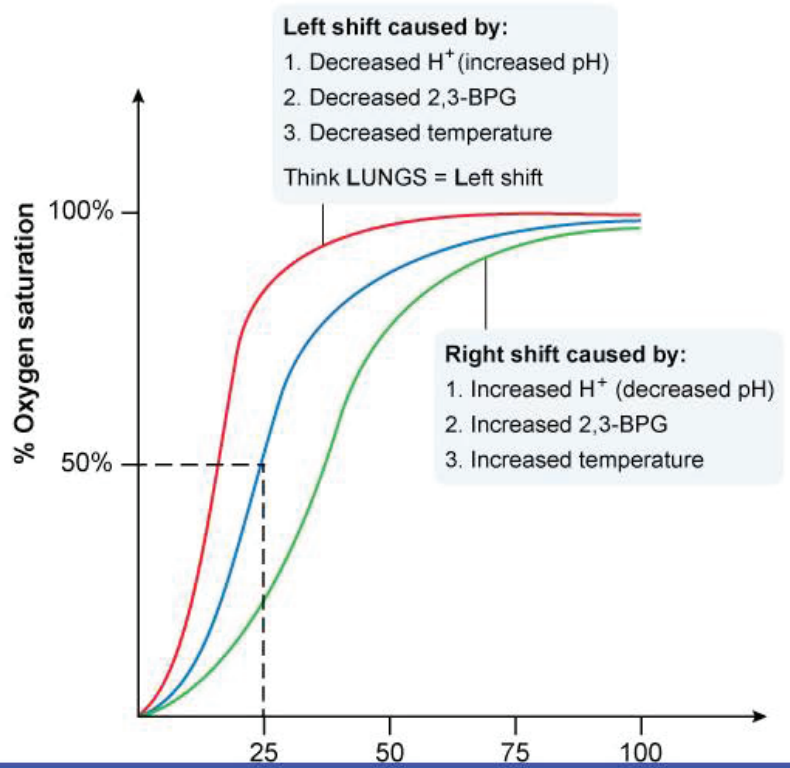
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Explanation

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Oxygen-hemoglobin dissociation curve



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The **oxygen-hemoglobin dissociation curve** describes the relationship between the partial pressure of oxygen in the blood and the oxygen saturation of hemoglobin. The partial pressure of oxygen at which hemoglobin is 50% saturated ($\mathbf{P_{50}}$) is a value used as a conventional measure of hemoglobin's affinity for oxygen. The P_{50} is about 26 mm Hg in normal individuals. A P_{50} **shift from 26 to 20 mm Hg** indicates that the affinity of hemoglobin for oxygen is increased (left shift of the oxygen dissociation curve).

Mutations that cause production of hemoglobin with **high oxygen affinity** (eg, hemoglobins Chesapeake and Kempsey) reduce the ability of hemoglobin to release oxygen within the peripheral tissues. Low oxygen levels stimulate the kidneys to increase erythropoietin synthesis, which results in a **compensatory erythrocytosis** that helps maintain normal oxygen delivery. Therefore, patients with high oxygen affinity hemoglobins are typically asymptomatic.

(Choice B) Sickle cell disease can result in hypoxia-induced hemolysis due to the ability of deoxygenated hemoglobin S to polymerize and cause excessive erythrocyte sickling and irreversible cell membrane damage. The oxygen dissociation curve for hemoglobin S is shifted to the right (↓ oxygen affinity) due to the stabilizing effects of polymerization on the deoxygenated form.

(Choice C) Hereditary spherocytosis results from a variety of molecular defects involving erythrocyte

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(Choice C) Hereditary spherocytosis results from a variety of molecular defects involving erythrocyte structural proteins responsible for linking the plasma membrane to the cytoskeleton (eg, spectrin, ankyrin). The resulting membrane instability leads to the formation of spherocytes – small, rounded erythrocytes with increased susceptibility to lyse in hypotonic solutions.

(Choice D) Megaloblastic erythrocyte changes (↑ MCV) are characteristically seen in vitamin B_{12} and folic acid deficiency due to impaired DNA synthesis.

(Choice E) Individuals with glucose-6-phosphate dehydrogenase deficiency develop rapid hemolysis during periods of increased oxidant stress, such as when taking antimalarials or sulfonamides or after ingestion of fava beans.

Educational objective:

P_{50} refers to the partial pressure of oxygen at which hemoglobin is 50% saturated. Hemoglobins with high oxygen affinity have a decreased P_{50} that is represented by a leftward shift of the oxygen dissociation curve. The reduced ability to release oxygen within the peripheral tissues leads to renal hypoxia, increased erythropoietin synthesis, and compensatory erythrocytosis.

References

- Hemoglobins with high oxygen affinity leading to erythrocytosis. New variants and new concepts.

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A 70-year-old man develops progressive fatigue and easy bruising. He has had unintentional weight loss and episodic fevers. Physical examination shows splenomegaly and enlarged lymph nodes in the cervical, axillary, and inguinal regions. Complete blood count reveals anemia, thrombocytopenia, and leukocytosis. Peripheral blood smear shows an increased number of small, mature-appearing, abnormal lymphocytes, which express CD20 and kappa light chains. During treatment, the patient receives an agent that directly binds and inhibits BCL-2 protein. Which of the following is the most likely effect of this therapy on the abnormal cells?

A. Accumulation of ubiquitinated intracellular proteins (3%)
B. Greater susceptibility to cytotoxic T cells (3%)
C. Increased activation of caspases (78%)
D. Increased single-strand DNA breaks (1%)
E. Interruption of cell growth in S phase (9%)
F. Targeting of antibody-dependent cellular cytotoxicity (3%)

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This patient's lymphadenopathy, splenomegaly, and increased number of mature lymphocytes in the blood that express B-cell markers ($CD20^+$, kappa light chains) indicate **chronic lymphocytic leukemia** (CLL). This disease is characterized by the progressive accumulation of **mature B cells** in hematopoietic tissues (leading to anemia, thrombocytopenia, lymphadenopathy, and splenomegaly) and peripheral blood (leading to leukocytosis) due to genetic mutations that lengthen B-cell survival.

In most cases of CLL, B-cell survival is promoted by the **overexpression of BCL-2** on the mitochondrial membrane. BCL-2 is an **antiapoptotic** protein that prevents stress signals from triggering the intrinsic apoptotic cascade, which is mediated by the release of cytochrome c from the mitochondria and the subsequent activation of caspases. Treatment of CLL with **BCL-2 inhibitors** (eg, venetoclax) makes tumor cells more sensitive to stress signals (eg, chemotherapy) by **increasing the activation of caspases**, which leads to cell death.

(Choice A) Bortezomib, a proteasome inhibitor that prevents the destruction of ubiquinated intracellular proteins, can be used against neoplasms that generate excessive amounts of protein (eg, multiple myeloma).

(Choice B) Because cancer cells produce new antigens (neoantigens) not seen in normal cells, they generally have mutations that allow them to evade cytotoxic T-cell detection. Immune checkpoint inhibitors,

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myeloma).

(Choice B) Because cancer cells produce new antigens (neoantigens) not seen in normal cells, they generally have mutations that allow them to evade cytotoxic T-cell detection. Immune checkpoint inhibitors, such as antibodies against PD-1 (eg, pembrolizumab) or CTLA-4, prevent cancer cells from evading cytotoxic T-cell detection.

(Choice D) Olaparib inhibits poly-ADP ribose polymerase, the enzyme that mediates the repair of single-strand DNA breaks. It is often used to treat breast, ovarian, or prostate cancer in individuals with BRCA mutations.

(Choice E) Many forms of chemotherapy target rapidly dividing cells by inhibiting DNA replication during S phase (eg, purine analogs). BCL-2 does not mediate DNA replication or repair.

(Choice F) Rituximab is a monoclonal antibody against the B-cell surface marker CD20. Although it is often used for CLL, it mediates cell death by binding to the B-cell surface (antibody-mediated cytotoxicity).

Educational objective:
Chronic lymphocytic leukemia is associated with overexpression of BCL-2, an anti-apoptotic protein, on the mitochondrial membrane. Treatment with a BCL inhibitor causes cancer cell death by promoting cytochrome c release from the mitochondria, which subsequently activates caspases.

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A newborn girl is admitted to the neonatal intensive care unit with jaundice, hepatomegaly, and generalized edema. She was born by vaginal delivery to a 32-year-old woman, gravida 2, para 2, who received minimal prenatal care. The infant's laboratory results show a hemoglobin level of 6 g/dL and a positive direct Coombs test. A peripheral blood smear shows many nucleated erythrocytes. The infant has significant respiratory distress due to pleural effusions and ascites and dies soon after birth. Autopsy shows areas of extramedullary hematopoiesis in many tissues. Which of the following is the most likely cause of this patient's condition?

A. ~~Abnormal hemoglobin polymerization~~ (2%)

B. ~~Absence of alpha globin chains~~ (7%)

C. Erythrocyte opsonization by maternal antibodies (76%)

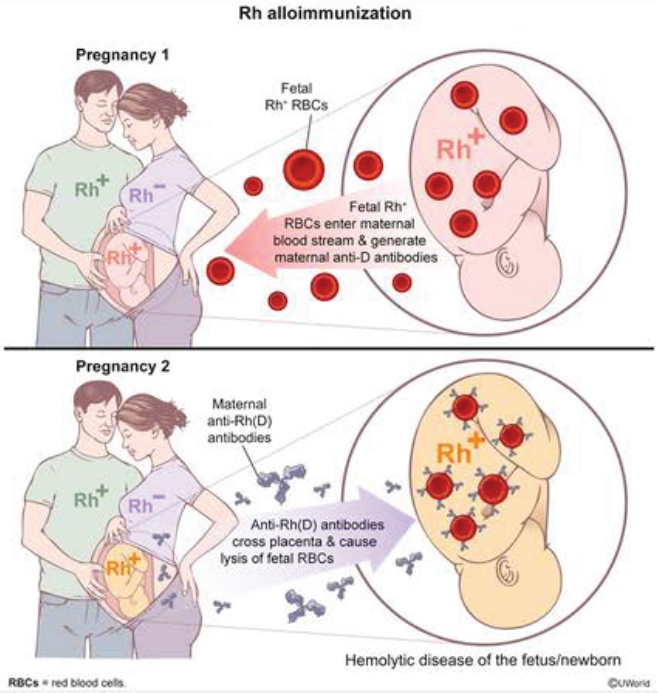
D. ~~Glucose-6-phosphate dehydrogenase deficiency~~ (2%)

E. Red blood cell lysis by fetal antibodies (11%)

76% 02 mins 03 secs 08/17/2020

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Hemolytic disease of the newborn (erythroblastosis fetalis) results from the **destruction of fetal red blood cells** by maternal antibodies directed against fetal erythrocyte antigens. These antibodies are **IgG antibodies**, the only class of antibody able to cross the placenta. Erythroblastosis fetalis is most commonly caused by Rhesus (Rh) incompatibility (particularly the D antigen).

Rh sensitization can occur in an **Rh(D)− mother** during pregnancy with an **Rh(D)+ fetus** due to small amounts of fetal blood crossing the placenta and entering the maternal circulation. These erythrocytes are viewed as foreign by the maternal immune system and induce the production of anti-Rh(D) IgG antibodies. In **subsequent pregnancies** with an Rh(D)+ fetus, these **antibodies cross the placenta** and opsonize fetal erythrocytes, causing hemolysis. This results in a positive direct Coombs test (indicating autoimmune hemolysis), profound **anemia, jaundice** (possibly leading to kernicterus), and generalized edema (**hydrops fetalis** due to accumulation of interstitial fluid). The severe anemia also stimulates release of immature, nucleated erythrocytes and leads to persistent extramedullary hematopoiesis in the liver, spleen, and other tissues (hepatosplenomegaly).

(Choice A) Sickle cell anemia causes vasoocclusion due to abnormal hemoglobin polymerization. It is asymptomatic in the fetus/neonate due to high levels of fetal hemoglobin that are not replaced by hemoglobin S until age 3-12 months.

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(Choice B) Fetuses with homozygous alpha-thalassemia (hemoglobin Barts) have no alpha globin chains and therefore form gamma-4 tetramers with very high oxygen affinity. The consequence is severe functional anemia and tissue hypoxia, which results in high-output heart failure and nonimmune hydrops fetalis (negative Coombs test).

(Choice D) Glucose-6-phosphate dehydrogenase deficiency can cause prolonged neonatal jaundice (beyond 2 weeks) due to increased erythrocyte breakdown and immaturity of the newborn liver. However, the associated anemia is rarely severe.

(Choice E) Infants are born with an immature immune system; their humoral defense during the first 6 months of life comes primarily from maternal circulating IgG that is received transplacentally prior to birth and from mucosal IgA received via breastfeeding. Therefore, fetal antibody-mediated red blood cell lysis is an unlikely etiology.

Educational objective:
Hemolytic disease of the newborn most commonly occurs from maternal sensitization to Rh antigens during a prior pregnancy with an Rh(D)+ fetus. In subsequent Rh(D)+ pregnancies, maternal anti-Rh(D) IgG antibodies cross the placenta and cause a severe autoimmune hemolytic anemia in the fetus and life-threatening hydrops fetalis.

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A 62-year-old woman is evaluated for refractory nausea and vomiting. She was recently diagnosed with ovarian cancer and underwent total hysterectomy with bilateral salpingo-oophorectomy and pelvic lymph node dissection. The patient was started on highly emetogenic adjuvant chemotherapy. Despite taking ondansetron around the clock, she continues to have nausea and vomiting. She has no abdominal pain or constipation. Vital signs are normal. Examination shows a well-healed abdominal scar. There is no tenderness or abnormal masses. Bowel sounds are normal. Additional therapy blocking which of the following receptors would most likely be helpful in this patient?

A. Endogenous opioid (16%)
B. Motilin (14%)
C. Neurokinin 1 (33%)
D. Neuropeptide Y (24%)
E. Nicotinic acetylcholine (10%)

33% 48 secs 11/15/2020

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Characteristics of antiemetic drugs		
Drug class	**Examples**	**Clinical uses**
Antimuscarinics (anticholinergics)	• Scopolamine	Motion sickness Hyperemesis gravidarum (promethazine)
Antihistamines	• Diphenhydramine • Meclizine • Promethazine	
Dopamine receptor antagonists	• Prochlorperazine • Metoclopramide	Chemotherapy-induced emesis
Serotonin (5-HT_3) receptor antagonists	• Ondansetron • Granisetron	
Neurokinin 1 (NK1) receptor antagonists	• Aprepitant • Fosaprepitant	

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Vomiting is a reflex that can be activated by either humoral or neuronal stimuli. The **area postrema** in the fourth ventricle has a chemoreceptor trigger zone that can respond to many neurotransmitters, drugs, or toxins. The **nucleus tractus solitarius** (NTS) in the medulla receives information from the area postrema, gastrointestinal tract via the vagus nerve, vestibular system, and central nervous system (eg, meninges, hypothalamus). Neurons from the NTS project to other medullary nuclei and coordinate the vomiting process.

The 5 major receptors involved in stimulating the vomiting reflex in the area postrema and adjacent vomiting center nuclei are M_1 muscarinic, D_2 dopaminergic, H_1 histaminic, 5-HT_3 serotonergic, and neurokinin 1 (NK1) receptors. **5-HT3 receptor antagonists** (eg, ondansetron) and dopamine receptor antagonists (eg, metoclopramide) are particularly helpful for chemotherapy-induced vomiting. When these do not control symptoms, **NK1 receptor antagonists** (prevent substance P release) can be considered; they prevent both acute vomiting and delayed emesis associated with chemotherapy.

(Choice A) Opioid receptor antagonists (eg, naltrexone) competitively bind opioid receptors to prevent action of endogenous or exogenous opioids. They are used mainly for opioid dependence.

(Choice B) Motilin regulates interdigestive migrating contractions. Erythromycin is a motilin receptor

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(Choice A) Opioid receptor antagonists (eg, naltrexone) competitively bind opioid receptors to prevent action of endogenous or exogenous opioids. They are used mainly for opioid dependence.

(Choice B) Motilin regulates interdigestive migrating contractions. Erythromycin is a motilin receptor agonist used for gastroparesis.

(Choice D) Neuropeptide Y is a polypeptide neurotransmitter found in the central and autonomic nervous systems. It is thought to play a role in appetite and pain perception. Neuropeptide Y antagonists have been investigated as potential antiobesity drugs.

(Choice E) Nicotinic antagonists are primarily used for muscle paralysis during surgery. Some antihistamines (eg, promethazine, meclizine) and antimuscarinics (eg, scopolamine) have anticholinergic activity and inhibitory effects on both the vomiting center and vestibular apparatus (useful for motion sickness).

Educational objective:

Vomiting is a reflex regulated mainly by 5 receptors, including M_1 muscarinic, D_2 dopaminergic, H_1 histaminic, 5-HT_3 serotonergic, and neurokinin 1 (NK1) receptors. 5-HT_3 and NK1 receptor antagonists are particularly useful for chemotherapy-induced vomiting.

References

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A 72-year-old woman is brought to the emergency department due to severe shortness of breath, tachypnea, and pleuritic-type chest pain. She had a similar episode 3 weeks ago and has been treated with warfarin since then. The patient has several other medical conditions and is taking all her medications as recommended. On examination, her temperature is 36.7 C (98 F), blood pressure is 120/60 mm Hg, pulse is 118/min, and respirations are 28/min. Pulse oximetry is 93% on room air. Laboratory results are notable for the following:

Coagulation studies	
Prothrombin time (PT)	18 sec
International Normalized Ratio (INR)	1.6

The patient's INR is subtherapeutic compared to her target INR range of 2.0-3.0 with warfarin. This patient is most likely taking which of the following additional medications?

A. ~~Acetaminophen~~ (1%)

B. ~~Amiodarone~~ (5%)

C. ~~Aspirin~~ (10%)

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International Normalized Ratio (INR) 1.0

The patient's INR is subtherapeutic compared to her target INR range of 2.0-3.0 with warfarin. This patient is most likely taking which of the following additional medications?

A. ~~Acetaminophen~~ (1%)
B. ~~Amiodarone~~ (5%)
C. ~~Aspirin~~ (10%)
D. ~~Cimetidine~~ (16%)
E. Diazepam (1%)
F. Indomethacin (1%)
G. Metronidazole (2%)
H. Oxycodone (0%)
I. Phenytoin (59%)

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Drugs/supplements that affect warfarin metabolism (selected)	
CYP450 Inhibitors ↑ Warfarin effect (↑ bleeding risk)	• Antibiotics (eg, metronidazole, macrolides) • Azole antifungals • Amiodarone • Cimetidine • Grapefruit juice
CYP450 Inducers ↓ Warfarin effect (↓ in efficacy)	• Carbamazepine • Phenytoin • Phenobarbital • Rifampin • St. John's wort

CYP450 = cytochrome P-450.

This patient with pleuritic chest pain, dyspnea, tachypnea, tachycardia, and hypoxia most likely experienced a **recurrent pulmonary embolism** (PE) in the setting of a **subtherapeutic INR level**, reflecting decreased warfarin efficacy. **Warfarin** is an oral anticoagulant that inhibits activation of vitamin K–dependent clotting factors, particularly factor VII. As a result, warfarin administration leads to

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CYP450 = cytochrome P-450.

This patient with pleuritic chest pain, dyspnea, tachypnea, tachycardia, and hypoxia most likely experienced a **recurrent pulmonary embolism** (PE) in the setting of a **subtherapeutic INR level**, reflecting decreased warfarin efficacy. **Warfarin** is an oral anticoagulant that inhibits activation of vitamin K–dependent clotting factors, particularly factor VII. As a result, warfarin administration leads to prolongation of the prothrombin time (PT) and INR (ratio of a patient's PT compared to a normal control). In patients with atrial fibrillation, deep venous thrombosis, or PE who are taking warfarin for anticoagulation, the dose is usually adjusted to achieve a target therapeutic INR range (generally 2.0-3.0).

Precise dosing of warfarin can be difficult due to its many interactions with other drugs that affect cytochrome P-450 activity, plasma protein binding, and/or gastrointestinal absorption. Warfarin elimination occurs primarily through hepatic metabolism by cytochrome P-450 enzymes. Drugs that **increase P-450 activity**, such as **phenytoin**, phenobarbital, and rifampin, **increase warfarin elimination** and decrease its anticoagulant activity (reflected as a subtherapeutic INR <2.0). Cholestyramine binds warfarin (and other drugs) in the intestine, thereby decreasing warfarin's therapeutic effect.

(Choices A, C, and F) When used concurrently with warfarin, aspirin and other nonsteroidal anti-inflammatory drugs such as indomethacin increase the risk of bleeding due to antiplatelet effects and gastrointestinal ulceration. These drugs can also displace warfarin from plasma protein binding sites

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(Choices A, C, and F) When used concurrently with warfarin, aspirin and other nonsteroidal anti-inflammatory drugs such as indomethacin increase the risk of bleeding due to antiplatelet effects and gastrointestinal ulceration. These drugs can also displace warfarin from plasma protein binding sites (increasing the concentration of free warfarin). Acetaminophen can interfere with vitamin K metabolism and enhance the effect of warfarin.

(Choices B, D, and G) Both cimetidine and amiodarone inhibit the metabolism of warfarin, which can result in an increased PT/INR and bleeding risk. The interaction between amiodarone and warfarin is important because some patients with atrial fibrillation may be prescribed both medications. The commonly used antibiotics metronidazole and trimethoprim-sulfamethoxazole also inhibit warfarin metabolism.

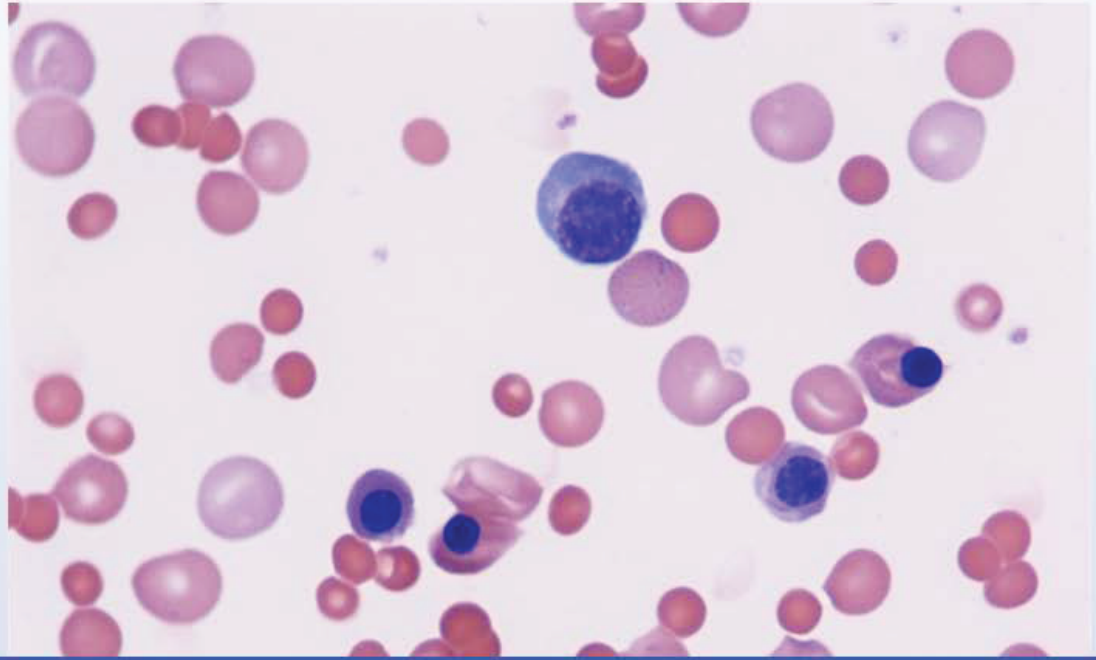
(Choices E and H) Benzodiazepines and opiates usually do not interact significantly with warfarin.

Educational objective:
Rifampin, phenobarbital, and phenytoin are potent enhancers of the cytochrome P-450 pathway; concurrent use of warfarin with these medications results in decreased efficacy of warfarin. In contrast, cimetidine, amiodarone, and trimethoprim-sulfamethoxazole inhibit warfarin metabolism, increasing the risk of bleeding.

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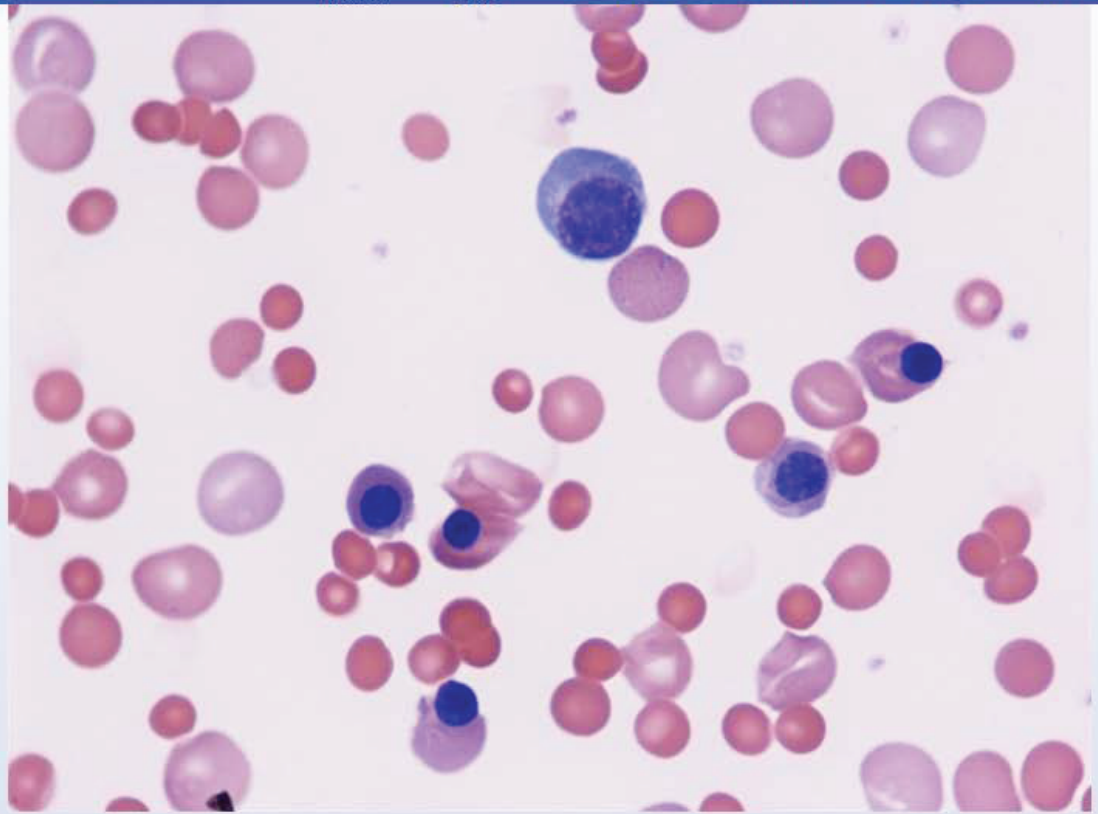
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A 32-year-old woman comes to the office due to worsening fatigue and exercise intolerance. She has no history of blood disorders. Physical examination shows mild mucosal pallor. Hemoglobin is 7.8 g/dL. Peripheral blood smear is shown in the image below.



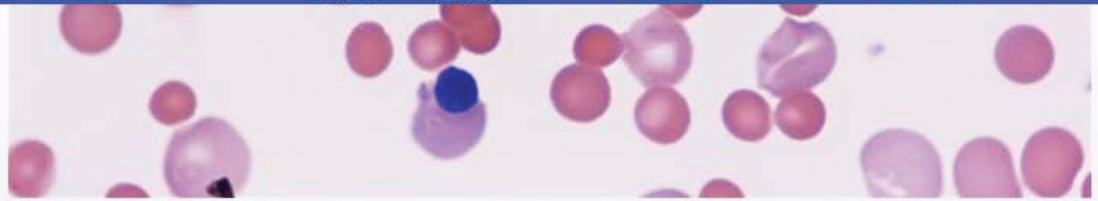
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Which of the following is the most likely cause of this patient's anemia?

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Which of the following is the most likely cause of this patient's anemia?

- A. Erythropoietin deficiency (7%)
- ✓ B. Hemolytic anemia (38%)
- C. ~~Iron deficiency anemia~~ (31%)
- D. Thrombotic microangiopathy (6%)
- E. ~~Vitamin B_{12} deficiency~~ (16%)

Correct

38%
Answered correctly

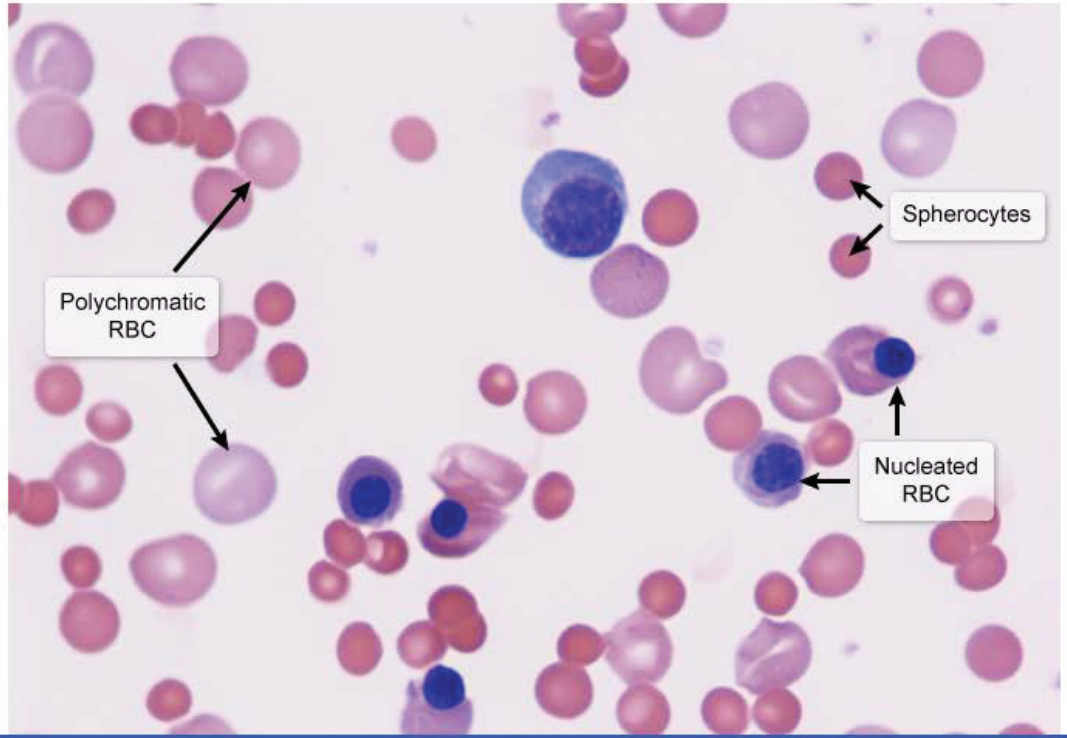
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Peripheral blood smear



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This patient with **symptomatic anemia** (eg, fatigue, exercise intolerance) has peripheral blood smear findings that indicate **hemolytic anemia**, including the following:

- **Increased reticulocytes:** Reticulocytes are larger than mature red blood cells (RBCs), lack central pallor, and have a bluish coloration (**polychromatic RBCs**) due to the presence of ribosomes, which are not found in mature RBCs. Increased reticulocytes in the peripheral blood is a nonspecific finding that indicates the bone marrow is responding appropriately to anemia by increasing production of new erythrocytes.
- **Spherocytes:** Spherocytes are erythrocytes with reduced cell membrane, which makes the cell spherical rather than biconcave. In otherwise healthy individuals, spherocytes generally arise in the setting of **immune-mediated** hemolytic anemia; in this condition, IgG-coated erythrocytes are partially phagocytized by splenic macrophages, which reduces the surface area of the erythrocyte cell membrane, thereby causing the erythrocyte to assume a spherical shape.
- **Nucleated erythrocytes:** Nucleated erythrocytes are very immature RBCs. The presence of nucleated RBCs in the peripheral blood indicates a strong bone marrow response to compensate for the anemia.

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(Choice A) Anemia due to erythropoietin deficiency is often seen in patients with end-stage renal disease because erythropoietin production by the kidneys is impaired. Individuals with erythropoietin deficiency are not able to sufficiently increase erythrocytosis in response to anemia; therefore, peripheral blood smear does not typically show increased reticulocytes or nucleated RBCs.

(Choice C) Iron deficiency anemia can be seen in young women with heavy menstruation or gastrointestinal bleeding. However, peripheral blood smear typically shows hypochromatic RBCs and microcytosis.

(Choice D) Thrombotic microangiopathy is associated with microvascular clot formation, which causes anemia via RBC shearing. In this condition, peripheral blood smear typically shows schistocytes, not spherocytes.

(Choice E) Vitamin B_{12} deficiency is common in patients with atrophic gastritis and alcoholism. It commonly causes macrocytic anemia with hypersegmented neutrophils on peripheral blood smear.

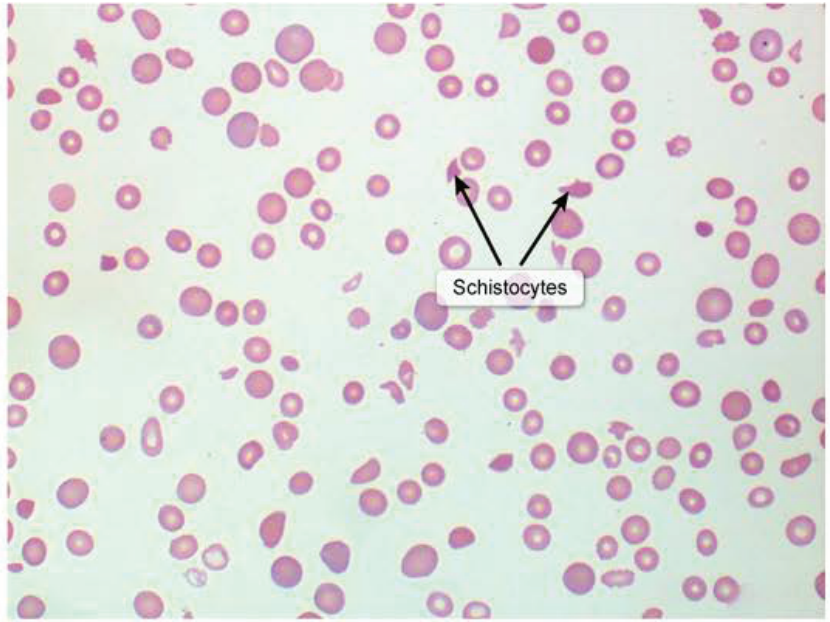
Educational objective:
In patients with hemolytic anemia, peripheral blood smear usually reveals evidence of reticulocytosis, spherocytes, and nucleated red blood cells.

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Microangiopathic hemolytic anemia



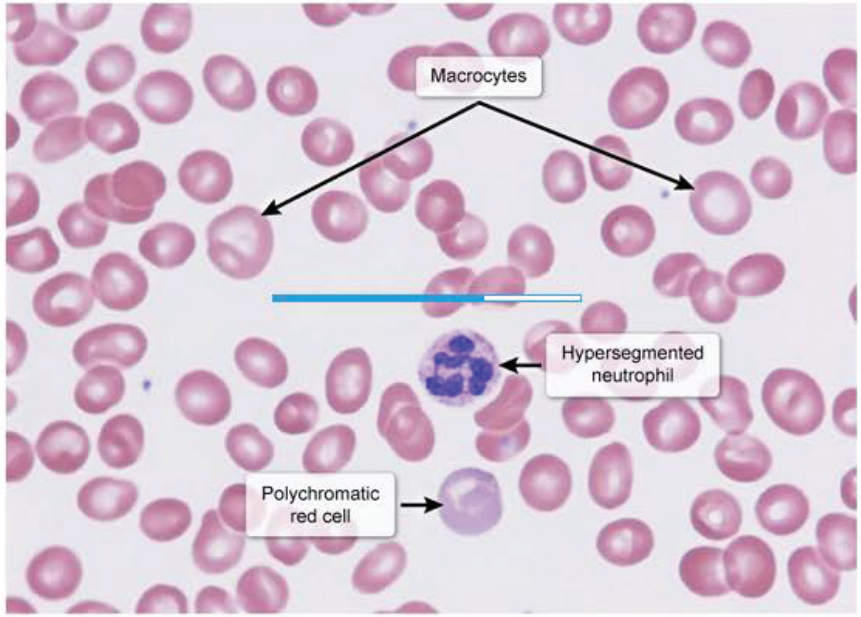
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Macrocytic anemia



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A 32-year-old man comes to the office due to progressive fatigue, easy bruising, and recurring episodes of gum bleeding. Physical examination shows several ecchymoses in his lower extremities. Laboratory studies are as follows:

Complete blood count	
Hemoglobin	7.8 g/dL
Platelets	65,000/mm^3
Leukocytes	3,000/mm^3
Coagulation studies	
Prothrombin time	22 sec
Activated partial thromboplastin time	53 sec
Plasma fibrinogen	134 mg/dL (normal: 200-400 mg/dL)

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Leukocytes	3,000/mm^3
Coagulation studies	
Prothrombin time	22 sec
Activated partial thromboplastin time	53 sec
Plasma fibrinogen	134 mg/dL (normal: 200-400 mg/dL)
D-dimer	4.1 µg/dL (normal: <0.5 µg/dL)

Bone marrow biopsy is performed and fluorescence in situ hybridization studies reveal a balanced translocation between the long arms of chromosomes 15 and 17. Which of the following proteins is most likely to be abnormal in the hematopoietic cells of this patient?

A. Epidermal growth factor receptor (4%)

B. GTP-binding protein (5%)

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μg/dL)

Bone marrow biopsy is performed and fluorescence in situ hybridization studies reveal a balanced translocation between the long arms of chromosomes 15 and 17. Which of the following proteins is most likely to be abnormal in the hematopoietic cells of this patient?

A. Epidermal growth factor receptor (4%)
B. GTP-binding protein (5%)
C. Platelet-derived growth factor receptor (14%)
D. Retinoblastoma gene product (3%)
E. Retinoic acid receptor (71%)

Correct

71%
Answered correctly

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Explanation

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Acute myelogenous leukemia (AML), characterized by failure of immature myeloid precursors (myeloblasts) to differentiate into mature granulocytes, is divided into 8 types (M0 through M7). **Acute promyelocytic leukemia** (APML), the M3 variant of AML, is associated with the **t(15;17)** cytogenetic translocation involving the promyelocytic leukemia (*PML*) gene on chromosome 15 and the retinoic acid receptor alpha (*RARA*) gene on chromosome 17. Fusion of these 2 genes produces ***PML/RARA***, a chimeric gene (illustrated in this fluorescence in situ hybridization image) that codes for an abnormal **retinoic acid receptor**, which then inhibits myeloblast differentiation. Abnormal promyelocytes and Auer rods are seen on the smear.

The clinical manifestations of AML, including anemia (fatigue, pallor), thrombocytopenia (petechiae, hemorrhages), and neutropenia (fever, opportunistic infections), result from marrow replacement by leukemic cells. As seen in this patient, APML is associated with **disseminated intravascular coagulation (DIC)**, which is characterized by activation of the coagulation cascade. Laboratory findings seen in DIC include thrombocytopenia, elevated D-dimer due to fibrinolysis, and prolonged coagulation profile times (eg, prothrombin time, activated partial thromboplastin time) and low fibrinogen due to consumption.

All-trans retinoic acid is used for treatment of APML.

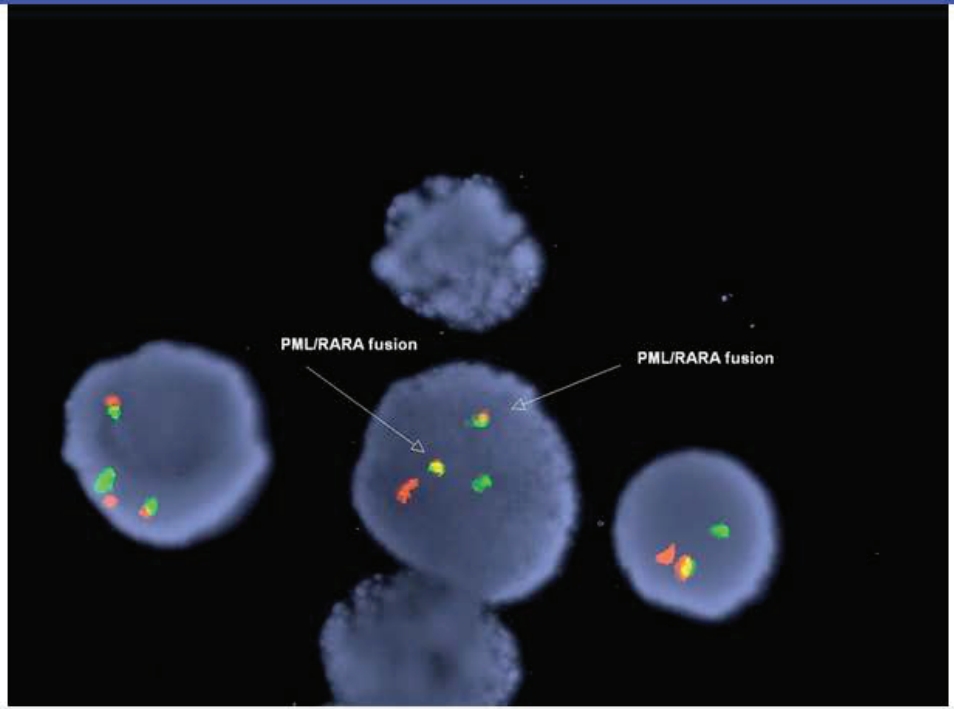
(Choice A) Mutations in the genes that code for the epidermal growth factor receptors are associated with certain lung (*ERBB1*), breast (*ERBB2*, also known as *HER2/neu*), ovarian, and gastric tumors

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Acute myelogenous leukemia (AML), characterized by failure of immature myeloid precursors (myeloblasts)

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certain lung (*ERBB1*), breast (*ERBB2*, also known as *HER2/neu*), ovarian, and gastric tumors

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include thrombocytopenia, elevated D-dimer due to fibrinolysis, and prolonged coagulation profile times (eg, prothrombin time, activated partial thromboplastin time) and low fibrinogen due to consumption.

All-trans retinoic acid is used for treatment of APML.

(Choice A) Mutations in the genes that code for the epidermal growth factor receptors are associated with certain lung (*ERBB1*), breast (*ERBB2*, also known as *HER2/neu*), ovarian, and gastric tumors.

(Choice B) GTP-binding proteins are involved in cellular signal transduction.

(Choice C) A defective platelet-derived growth factor receptor plays a role in the pathogenesis of several cancers, including ovarian cancers.

(Choice D) An abnormal *RB* gene predisposes to development of retinoblastoma and osteosarcoma.

Educational objective:
The cytogenetic defect t(15;17) is associated with acute promyelocytic leukemia (APML). A translocation involving the retinoic acid receptor alpha (*RARA*) gene from chromosome 17 and the promyelocytic leukemia (*PML*) gene on chromosome 15 leads to the formation of *PML/RARA*, a fusion gene whose product inhibits differentiation of myeloblasts and triggers the development of APML.

Pathology Hematology & Oncology Acute promyelocytic leukemia

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A 45-year-old man comes to the office due to 3 months of exertional fatigue and weight loss. He is sexually active with multiple male partners. Temperature is 37.9 C (100.2 F), blood pressure is 110/70 mm Hg, pulse is 84/min, and respirations are 13/min. BMI is 20 kg/m^2. The patient appears chronically ill and has mucosal pallor. There are thick, white plaques over the buccal mucosa and soft palate. Anterior and posterior cervical lymphadenopathy is present. The lungs are clear to auscultation. The abdomen is soft and nontender. There is no organomegaly. Laboratory results are as follows:

Hematocrit	28%	
Mean corpuscular volume	76 µm^3	
Platelets	160,000/mm^3	
Leukocytes	4,100/mm^3	
Iron, serum	30 µg/dL	
Total iron-binding capacity	190 µg/dL	(normal: 250-460)

Which of the following is the most likely underlying cause of this patient's anemia?

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Platelets	160,000/mm^3	
Leukocytes	4,100/mm^3	
Iron, serum	30 µg/dL	
Total iron-binding capacity	190 µg/dL	(normal: 250-460)

Which of the following is the most likely underlying cause of this patient's anemia?

- A. Abnormal iron utilization (67%)
- B. Decreased synthesis of globin chains (6%)
- C. Deposition of fibrin in the microcirculation (2%)
- D. Gastrointestinal blood loss (16%)
- E. Deficiency of a heme synthesis enzyme (6%)

Correct

67% Answered correctly

03 mins, 56 secs Time Spent

01/24/2021 Last Updated

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Anemia of chronic disease	
Pathogenesis	• ↑ inflammatory cytokines (eg, hepcidin) • Inhibition of ferroportin on enterocytes and macrophages • ↓ iron absorption and ↑ iron sequestration • Reduced circulating iron → impaired erythropoiesis
Common Etiologies	• Malignancy • Chronic infection • Rheumatic disease • Obesity • Diabetes mellitus • Congestive heart failure
Laboratory findings	• Normocytic/slightly microcytic anemia • ↓ serum iron, iron-binding capacity, reticulocyte count • ↑ bone marrow iron • Lower than expected erythropoietin for degree of anemia
Treatment	• Treat underlying condition causing inflammation

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Treatment	• Treat underlying condition causing inflammation

This patient's high-risk sexual history, weight loss, lymphadenopathy, chronically ill appearance, and oral candidiasis (white buccal/soft palate plaques) suggest undiagnosed HIV infection. Patients with chronic infections such as HIV often develop **anemia of chronic disease** (ACD) due to high circulating levels of inflammatory cytokines, which cause maladaptive **changes to iron utilization**.

Although ACD is mediated by a wide range of inflammatory cytokines (eg, IL-1, IL-6, tumor necrosis factor-alpha, interferon gamma), the major player is **hepcidin**, a small peptide released by the liver in response to inflammation. Hepcidin binds to and inhibits iron channels on enterocytes and reticuloendothelial macrophages, leading to reduced iron absorption in the gut and reduced iron recycling in the reticuloendothelial system (the site of senescent erythrocyte destruction). This significantly **reduces circulating serum iron**, which limits iron availability for erythropoiesis.

Patients with ACD typically develop normocytic or **slightly microcytic anemia** with a low reticulocyte response. **Total iron-binding** capacity is generally **reduced** due to cytokine-mediated suppression of transferrin. Treatment of the underlying condition (eg, antiretroviral therapy) often ameliorates or resolves ACD.

(Choice B) Decreased synthesis of globin chains is seen in thalassemia, a genetic disorder that presents

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transferrin. Treatment of the underlying condition (eg, antiretroviral therapy) often ameliorates or resolves ACD.

(Choice B) Decreased synthesis of globin chains is seen in thalassemia, a genetic disorder that presents with microcytic anemia and reduced erythrocyte life span. Serum iron levels tend to be high with thalassemia due to increased erythropoiesis to compensate for the anemia.

(Choice C) Fibrin deposition in the microvasculature is seen in disseminated intravascular coagulation, a consumptive coagulopathy marked by microangiopathic hemolytic anemia and significant thrombocytopenia. Patients typically have normocytic (not microcytic) anemia and normal or high serum iron levels.

(Choice D) Iron deficiency anemia (eg, gastrointestinal bleeding) also typically causes microcytic anemia with low serum iron. However, unlike ACD, iron deficiency anemia is typically associated with a high iron-binding capacity due to increased circulating transferrin levels.

(Choice E) Porphyria is a genetic disorder caused by deficiency of heme synthesis enzymes. Patients typically develop neurovisceral (eg, abdominal pain) or cutaneous (eg, blistering) manifestations. Microcytic anemia with low serum iron would be atypical.

Educational objective:

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consumptive coagulopathy marked by microangiopathic hemolytic anemia and significant thrombocytopenia. Patients typically have normocytic (not microcytic) anemia and normal or high serum iron levels.

(Choice D) Iron deficiency anemia (eg, gastrointestinal bleeding) also typically causes microcytic anemia with low serum iron. However, unlike ACD, iron deficiency anemia is typically associated with a high iron-binding capacity due to increased circulating transferrin levels.

(Choice E) Porphyria is a genetic disorder caused by deficiency of heme synthesis enzymes. Patients typically develop neurovisceral (eg, abdominal pain) or cutaneous (eg, blistering) manifestations. Microcytic anemia with low serum iron would be atypical.

Educational objective:
Anemia of chronic disease is caused by chronic elevations in inflammatory cytokines, which lead to reduced iron absorption and increased iron retention in the reticuloendothelial system. This impairs iron availability and causes a normocytic or slightly microcytic anemia with low serum iron and low total iron-binding capacity.

Pathophysiology	Hematology & Oncology	Anemia of inflammation
Subject	System	Topic

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A 23-year-old man comes to the office due to a rapidly enlarging left jaw mass that has developed over the past several weeks. The patient is a political refugee from East Africa. He has no known medical problems and takes no medications. Temperature is 37.1 C (98.8 F). Physical examination shows a large left-sided tumor on his jaw with surrounding lymphadenopathy but no erythema or warmth. The rest of the examination is unremarkable. HIV testing is negative. The lesion is biopsied, and numerous mitotic figures and apoptotic bodies are observed on histopathologic examination. Which of the following genetic features is most likely to be present in this tissue?

A. BCL2 overexpression (7%)

B. *BCR-ABL* rearrangement (3%)

C. c-*Myc* oncogene overexpression (85%)

D. n-*Myc* oncogene overexpression (1%)

E. Tyrosine kinase activation (1%)

85% 36 secs 11/06/2020

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This patient has the typical presentation of endemic (African-type) **Burkitt lymphoma**, of which jaw involvement is a characteristic feature. Almost all cases of endemic Burkitt lymphoma are associated with Epstein-Barr virus (EBV) infection. EBV has been implicated in the immortalization of lymphoma cells. Histologically, Burkitt lymphoma has a "starry sky" appearance due to the presence of macrophages and apoptotic bodies in a sea of medium-sized lymphocytes.

Up to 90% of Burkitt lymphoma cases are associated with translocation of the c-*Myc* gene on chromosome 8, usually onto the Ig heavy chain region of chromosome 14 **[t(8;14)].** This translocation leads to overexpression of the **c-*Myc*** oncogene and tumor growth. Burkitt lymphoma is a high-grade lymphoma. Although it is very aggressive, the tumor responds well to short-term, intensive high-dose chemotherapy. Patients with limited disease have an excellent prognosis.

(Choice A) In follicular lymphoma, there is overexpression of the antiapoptotic BCL2 as a result of the t(14;18) translocation. Follicular lymphoma causes generalized lymphadenopathy and tends to affect the elderly. Jaw involvement would be very unusual.

(Choices B and E) The *BCR-ABL* rearrangement is found in chronic myelogenous leukemia and some forms of acute lymphoblastic leukemia. The translocation causes increased tyrosine kinase activity.

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(Choices B and E) The *BCR-ABL* rearrangement is found in chronic myelogenous leukemia and some forms of acute lymphoblastic leukemia. The translocation causes increased tyrosine kinase activity.

(Choice D) Overexpression of the n-*Myc* oncogene is usually seen in neuroblastoma.

Educational objective:
Histologically, Burkitt lymphoma has a "starry sky" appearance due to the presence of macrophages and apoptotic bodies in a sea of medium-sized lymphocytes. The rates of mitosis and apoptosis in the cancerous tissue are high. Almost all cases of Burkitt lymphoma are associated with translocations of the c-*Myc* gene on chromosome 8, usually onto the Ig heavy chain region of chromosome 14 [t(8;14)].

Pathology Hematology & Oncology Burkitt lymphoma

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A 23-year-old woman is evaluated due to 10 days of nonproductive cough, low-grade fever, headache, and malaise. The patient has no other medical problems and takes no medications. Lung examination reveals scattered rales. Chest x-ray reveals bilateral patchy areas of consolidation. She has mild anemia and an elevated serum lactate dehydrogenase level. The patient is treated for presumed *Mycoplasma* pneumonia with azithromycin. Two months later, her symptoms and the anemia have resolved. Which of the following best explains the resolution of this patient's anemia?

A. Elimination of bacterial cell wall antigens (8%)
B. ~~Elimination of intraerythrocytic microorganisms~~ (12%)
C. Fading of immune response against the bacteria (59%)
D. ~~Replenishment of body iron stores~~ (14%)
E. ~~Replenishment of intracellular enzyme stores~~ (5%)

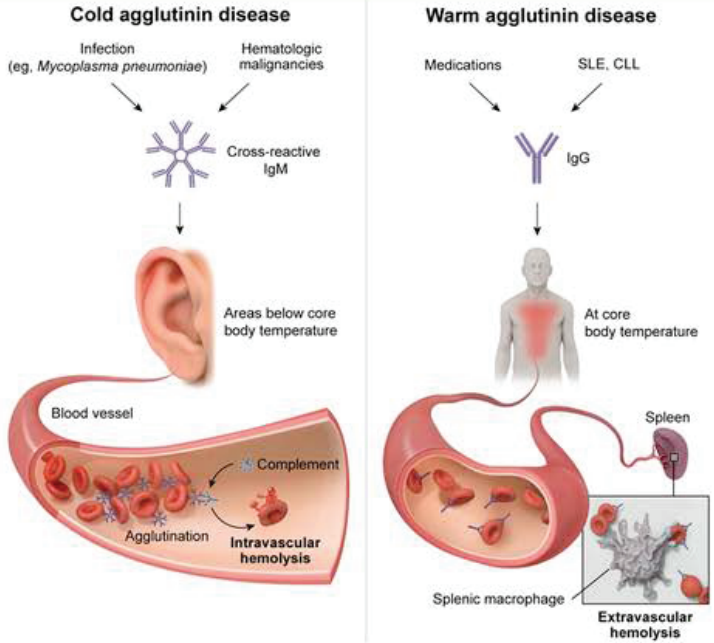
Correct

59% Answered correctly
02 mins, 08 secs Time Spent
09/05/2020 Last Updated

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Exhibit Display



CLL = chronic lymphocytic leukemia; **SLE** = systemic lupus erythematosus.

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Mycoplasma pneumoniae is a common cause of tracheobronchitis and walking pneumonia. It attacks the respiratory epithelium by binding to an oligosaccharide (**I-antigen**) that is also present on the surface of erythrocytes. This leads to the formation of **cross-reacting IgM antibodies** that attach to red blood cells, activate the complement system, and cause erythrocyte lysis.

The cross-reacting antibodies are called **cold agglutinins** because they bind to erythrocytes in areas where the blood temperature is below core body temperature (eg, distal extremities, nose). Most patients with cold agglutinins are asymptomatic, but some develop manifestations of intravascular **hemolytic anemia** such as elevated reticulocyte count and lactate dehydrogenase level. IgM titers usually begin to fall approximately 4 weeks after initial infection leading to a resolution of the hemolytic anemia (within 8 weeks).

Other extrapulmonary manifestations of *M pneumoniae* include Stevens-Johnson syndrome, joint pain, encephalitis, cardiac rhythm disturbances, and bullous myringitis.

(Choice A) *M pneumoniae* is an atypical bacterium; it has a plasma membrane composed of cholesterol (unlike most bacteria) and no cell wall. The lack of a cell wall makes this pathogen resistant to beta-lactam antibiotics.

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antibiotics.

(Choice B) Malaria and babesiosis are associated with intraerythrocytic organisms that can cause cell lysis and anemia. However, these pathogens usually cause high fever and more severe clinical syndromes. In addition, azithromycin monotherapy is not an effective cure for these infections.

(Choice D) Iron deficiency anemia, which is most commonly due to blood loss, can often be improved by replenishing body iron stores (eg, oral iron supplementation). Chronic infection or inflammatory conditions can be associated with anemia of chronic disease, which is due to impaired utilization of iron (not absolute iron deficiency).

(Choice E) Enzyme deficiencies that cause anemia include glucose-6-phosphate dehydrogenase (G6PD) deficiency and pyruvate kinase deficiency. Infection and medications that cause oxidative stress (eg, sulfonamides, antimalarial agents) can cause hemolysis in patients with G6PD; however, G6PD is an X-linked disorder (it is seen in men).

Educational objective:

Mycoplasma pneumoniae binds an oligosaccharide on the respiratory epithelium that is also present on erythrocytes, leading to the generation of cross-reacting IgM antibodies (cold agglutinins). Patients with *M pneumoniae* infections often develop mild, transient hemolytic anemia that resolves as IgM antibody titers decline (6-8 weeks after infection begins).

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Microbiology Hematology & Oncology Community-acquired pneumonia

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A 32-year-old African American male is diagnosed with acute prostatitis. He has no significant past medical history. He begins treatment with trimethoprim-sulfamethoxazole, but subsequently develops dark urine and anemia with a high reticulocyte count. Which of the following is the best explanation for the observed findings?

A. Antibody-mediated erythrocyte destruction (7%)
B. Hereditary erythrocyte membrane defect (3%)
C. Hereditary erythrocyte enzyme deficiency (77%)
D. Hemoglobin structure abnormality (4%)
E. Microangiopathic hemolytic anemia (6%)

Correct

77% Answered correctly

37 secs Time Spent

01/30/2021 Last Updated

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This patient is demonstrating signs of hemolysis induced by trimethoprim-sulfamethoxazole (Bactrim, TMP/SMX). This scenario is not an uncommon way for glucose-6-phosphate dehydrogenase (G6PD) deficiency to present. G6PD deficiency is an X-linked disorder that affects mostly males, and is more common in patients of African, Asian and Mediterranean descent. G6PD is an enzyme of the pentose phosphate pathway that in erythrocytes is essential for maintaining adequate concentrations of NADPH. Insufficient NADPH results in an inability to maintain glutathione in the reduced state. This increases the vulnerability of erythrocytes to oxidative stress and manifests with hemolysis induced by infection, drugs (e.g. bactrim, dapsone, antimalarials, nitrofurantoin), or other oxidants (e.g. fava beans).

Hemolytic episodes manifest with symptoms of anemia such as malaise and pallor, indirect bilirubinemia (jaundice), hemoglobinemia and hemoglobinuria (dark-red urine). The level of serum haptoglobin decreases and a reticulocytosis develops to compensate for the increased destruction of RBCs. Patients are generally asymptomatic between episodes.

(Choice A) Autoimmune hemolytic anemias result from extrinsic antibody-mediated hemolysis and are associated with a positive Coombs test. These anemias often accompany SLE and other autoimmune diseases, Hodgkin and non-Hodgkin lymphomas, *Mycoplasma* infections (cold agglutinins), and infectious mononucleosis.

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mononucleosis.

(Choice B) Hereditary spherocytosis is an autosomal dominant defect in RBC structural proteins (spectrin, ankyrin, or protein 4.1) characterized by increased erythrocyte osmotic fragility and MCHC (mean corpuscular hemoglobin concentration) increased above 36 g/dL.

(Choice D) Abnormalities of hemoglobin structure include hemoglobin S (sickle cell disease), C, and E disorders, as well as others. Heterozygotes usually show minimal to no clinical signs, while homozygotes present with hemolytic anemia in addition to other disease-specific complications.

(Choice E) Microangiopathic hemolytic anemia (MAHA) occurs when there is destruction of RBCs within small vessels due to widespread thrombosis. MAHA is associated with disseminated intravascular coagulation (DIC), thrombotic thrombocytopenic purpura (TTP) and hemolytic-uremic syndrome (HUS).

Educational Objective:
Glucose-6-phosphate dehydrogenase deficiency is an X-linked disorder of the hexose monophosphate (pentose phosphate) pathway. In affected individuals, the amount of NADPH produced in RBCs is low, which impairs glutathione-mediated inactivation of free radicals. Hemolytic episodes are induced by infections, medications, and other oxidants.

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A 52-year-old man comes to the physician complaining of dizziness, headaches, and pruritus after showering. He has smoked half a pack of cigarettes daily for the past fifteen years and drinks alcohol socially. Physical examination shows a reddish facial complexion and mild splenomegaly. Laboratory results are as follows:

Complete blood count

Hemoglobin	19 g/dL
Hematocrit	59%
Erythrocytes	7.5 million/µL
Platelets	550,000 /µL
Leukocytes	15,600 /µL

Which of the following is the most likely cause of this patient's findings?

A. ~~Decreased circulating plasma volume~~ (6%)

B. Decreased blood oxygen saturation (4%)

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Hemoglobin	19 g/dL
Hematocrit	59%
Erythrocytes	7.5 million/μL
Platelets	550,000 /μL
Leukocytes	15,600 /μL

Which of the following is the most likely cause of this patient's findings?

A. ~~Decreased circulating plasma volume~~ (6%)

B. Decreased blood oxygen saturation (4%)

C. Increased bone marrow sensitivity to growth factors (56%)

D. ~~Increased red blood cell life span~~ (3%)

E. Increased serum erythropoietin levels (29%)

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Explanation

Causes of polycythemia					
	Etiology	**Plasma volume**	**RBC mass**	**SaO_2**	**EPO level**
Relative polycythemia	Dehydration, excessive diureses	Decreased	Normal	Normal	Normal
Primary polycythemia*	Polycythemia vera	Increased	Increased	Normal	Decreased
Secondary polycythemia*	Physiologic (eg, hypoxia)	Normal	Increased	Decreased	Increased
	Inappropriate (eg, EPO-producing tumors)	Normal	Increased	Normal	Increased
* Primary & secondary polycythemias are absolute polycythemias.					

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Polycythemia vera (PV) is a clonal myeloproliferative disease of pluripotent hematopoietic stem cells. Approximately 95% of patients with PV have a V617F mutation involving the JAK2 gene, which is involved in signal transduction. This mutation replaces a valine with phenylalanine at the 617 position, rendering hematopoietic cells **more sensitive to growth factors** such as erythropoietin and thrombopoietin.

PV presents with **increased RBC mass**, increased plasma volume, and **low erythropoietin** levels. Additional manifestations can include an **elevated platelet** and/or **WBC count**, thrombotic events (from blood hyperviscosity), peptic ulceration and aquagenic pruritus (due to histamine release from basophils), and gouty arthritis (from increased cell turnover). Physical examination typically shows a plethoric, reddened face and splenomegaly. Diagnosis is established by confirming low serum erythropoietin levels and bone marrow aspiration cytogenetic studies showing a **JAK2 mutation**. Treatment involves serial phlebotomy as necessary to keep the hematocrit < 45%.

(Choice A) Dehydration or excessive diuresis can also cause elevated hematocrit, mild leukocytosis, and thrombocytosis due to low effective circulating volume. However, splenomegaly and symptoms such as pruritus would not be seen.

(Choice B) Hypoxia is a strong stimulus for erythropoietin production. SaO_2 < 92% (PaO_2 < 65 mm Hg)

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pruritus would not be seen.

(Choice B) Hypoxia is a strong stimulus for erythropoietin production. SaO_2 < 92% (PaO_2 < 65 mm Hg) appears to be the threshold for the development of (physiologic) secondary polycythemia. Conditions such as chronic obstructive pulmonary disease and obstructive sleep apnea can cause secondary polycythemia. However, these will not cause leukocytosis, thrombocytosis, or splenomegaly.

(Choice D) Increased red cell life span would not be expected to cause leukocytosis and thrombocytosis.

(Choice E) EPO-producing tumors (eg, renal cell carcinoma, hepatocellular carcinoma) can cause secondary polycythemia due to abnormal erythropoietin production. Workup will show an elevated erythropoietin level. However, the combination of multiple elevated cell lines and splenomegaly is unlikely to result from a process causing secondary polycythemia.

Educational objective:
Polycythemia vera (PV) is a clonal myeloproliferative disease characterize by an increased RBC mass, increased plasma volume, and low erythropoietin levels. PV can be differentiated from secondary polycythemia by the presence of leukocytosis, thrombocytosis, and/or splenomegaly. The majority of patients with PV have a JAK2 mutation rendering hematopoietic stem cells more sensitive to growth factors.

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A 34-year-old male notes a lump in his neck that has grown slowly over the past several months. His social history is significant for smoking one pack of cigarettes per day and occasional alcohol use. On review of systems, he denies dysphagia, chest pain, weight loss or fever. Biopsy of the mass reveals abnormal cells with the t(14;18) chromosomal translocation. This chromosomal change is most likely to cause which of the following abnormalities in gene expression?

- ✓ A. Bcl2 overexpression (64%)
- B. Bcr-abl hybrid formation (9%)
- C. ~~C-myc overexpression~~ (19%)
- D. ~~Erb-B2 overexpression~~ (2%)
- E. ~~p53 inactivation~~ (3%)

Correct

64% Answered correctly

01 min, 17 secs Time Spent

01/30/2021 Last Updated

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This patient has follicular lymphoma, a non-Hodgkin lymphoma of the cleaved and noncleaved B-lymphocytes of the follicular center. The classic cytogenetic abnormality in follicular lymphoma is the t(14;18) translocation, which moves the *Bcl*-2 (B-cell lymphoma-2) protooncogene from chromosome 18 to chromosome 14, near the site of the immunoglobulin heavy chain enhancer element. *Bcl*-2 is considered a protooncogene because it has anti-apoptotic effects (prevents the release of pro-apoptotic factors within affected cells). When this protooncogene is positioned near the immunoglobulin enhancer element, the resultant *Bcl*-2 overexpression allows for cell immortality.

(Choice B) The Bcr-abl hybrid is formed as a result of a reciprocal translocation between chromosomes 9 and 22 (the Philadelphia chromosome). This is the characteristic cytogenetic abnormality in chronic myelogenous leukemia (CML).

(Choice C) C-myc overexpression occurs in many malignancies. The myc oncogene is located on chromosome 8. Translocations between chromosome 8 and chromosomes coding for the immunoglobulin heavy chain (14), the kappa light chain (2), or the lambda light chain (22) may result in Burkitt lymphoma.

(Choice D) ErbB2, HER2 and neu are all names for the same epidermal growth factor receptor, which is overexpressed in many cases of breast cancer.

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(Choice C) C-myc overexpression occurs in many malignancies. The myc oncogene is located on chromosome 8. Translocations between chromosome 8 and chromosomes coding for the immunoglobulin heavy chain (14), the kappa light chain (2), or the lambda light chain (22) may result in Burkitt lymphoma.

(Choice D) ErbB2, HER2 and neu are all names for the same epidermal growth factor receptor, which is overexpressed in many cases of breast cancer.

(Choice E) p53 gene inactivation occurs as one of the two "hits" in many human malignancies. Normally, the p53 protein functions as a tumor suppressor. Li-Fraumeni syndrome is an autosomal dominant cancer syndrome caused by an inherited mutation in p53.

Educational Objective:

Follicular lymphoma is a non-Hodgkin lymphoma of follicular B-lymphocytes. Patients with follicular lymphoma characteristically have a translocation between chromosomes 14 and 18 which causes *Bcl*-2 overexpression. *Bcl*-2 is considered a protooncogene because it has anti-apoptotic effects.

Pathology	Hematology & Oncology	Nonhodgkin lymphoma
Subject	System	Topic

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A 12-month-old boy is brought to the office by his father due to prolonged bleeding from mouth after slipping and hitting his face on a coffee table. He was born at term, and his mother died shortly after his birth due to bleeding complications following a home delivery. Vital signs are normal. He is awake and alert. There is blood oozing from his gums and marked bruises along his trunk and thighs. The remainder of the physical examination is normal. Laboratory evaluation shows decreased von Willebrand Factor antigen levels and activity, measured via the ristocetin cofactor assay. Which of the following sets of laboratory values is most likely present in this patient?

	Platelets	PT	PTT	
A.	Decreased	Normal	Normal	(8%)
B.	Decreased	Prolonged	Prolonged	(3%)
✓ C.	Normal	Normal	Prolonged	(72%)
D.	Normal	Prolonged	Normal	(7%)
E.	Normal	Prolonged	Prolonged	(7%)

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Laboratory characteristics of coagulopathies				
	PT	**aPTT**	**Platelet count**	**Bleeding time**
Hemophilia A & B	Normal	↑	Normal	Normal
von Willebrand factor deficiency	Normal	Normal or ↑	Normal	↑
Disseminated intravascular coagulation	↑	↑	↓	↑
Uremic platelet dysfunction	Normal	Normal	Normal	↑
Heparin administration	Normal	↑	Normal (except in heparin-induced thrombocytopenia)	Normal

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coagulation				
Uremic platelet dysfunction	Normal	Normal	Normal	↑
Heparin administration	Normal	↑	Normal (except in heparin-induced thrombocytopenia)	Normal
Warfarin use	↑	↑ (weak effect)	Normal	Normal
Immune thrombocytopenia	Normal	Normal	↓	↑

aPTT = activated partial thromboplastin time; **PT** = prothrombin time.

Von Willebrand disease (vWD) is caused by genetic mutations that lead to decreased quantity or impaired function of **von Willebrand factor** (vWF), a multimeric glycoprotein produced by platelets and endothelial cells. VWF has 2 important hemostatic functions:

1. It binds platelets to vascular subendothelial components at sites of injury (and platelets to each other), which results in the formation of hemostatic platelet plugs. Therefore, patients with VWD have

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Von Willebrand disease (vWD) is caused by genetic mutations that lead to decreased quantity or impaired function of **von Willebrand factor** (vWF), a multimeric glycoprotein produced by platelets and endothelial cells. VWF has 2 important hemostatic functions:

1. It binds platelets to vascular subendothelial components at sites of injury (and platelets to each other), which results in the formation of hemostatic platelet plugs. Therefore, patients with VWD have impaired platelet aggregation but **normal platelet count** (as platelet consumption/production is unaffected).
2. VWF acts as a **carrier protein for factor VIII** and protects it from degradation. Because factor VIII is part of the intrinsic (contact activation) coagulation pathway, patients with VWD sometimes have **prolonged PTT** (due to increased destruction of factor VIII), but **PT will be normal**.

VWD is typically transmitted in an autosomal dominant fashion so a **family history** of bleeding is often an important diagnostic clue. Most cases are asymptomatic, but a minority (~1%) have easy bruising, skin bleeding, and bleeding from mucous membranes (eg, oropharyngeal, gastrointestinal, uterine). Testing for vWF level and activity (eg, ristocetin cofactor assay) can help confirm the diagnosis.

(Choice A) Primary immune thrombocytopenia (ITP) is an autoimmune disease associated with immune-mediated platelet destruction. Although patients with ITP often have easy bleeding, VWF levels and

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(Choice A) Primary immune thrombocytopenia (ITP) is an autoimmune disease associated with immune-mediated platelet destruction. Although patients with ITP often have easy bleeding, VWF levels and activity are normal, and a family history of bleeding is uncommon (as ITP is an acquired disorder). ITP is marked by thrombocytopenia and normal PT/PTT.

(Choice B) Disseminated intravascular coagulation is caused by widespread activation of coagulation and fibrinolysis due to sepsis, malignancy, trauma, or obstetric complication. It is an acquired disorder, so a family history of bleeding is uncommon. Disseminated intravascular coagulation is associated with low platelets and elevated PT and PTT.

(Choice D) Vitamin K deficiency and warfarin use impair synthesis of vitamin K–dependent clotting factors (II, VII, IX, and X), which leads to prolonged PT and normal platelet count and PTT (PTT can sometimes be mildly elevated). Although vitamin K deficiency is common in newborns, it is very uncommon in otherwise healthy children and adults. In addition, the family history of bleeding disorder makes this much less likely than vWD.

(Choice E) Patients with severe liver disease often have impaired hepatic synthetic function and are unable to generate sufficient quantities of clotting factors. Therefore, they often have elevated PT and PTT (with normal or low platelets). This otherwise healthy boy is unlikely to have significant liver disease

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(II, VII, IX, and X), which leads to prolonged PT and normal platelet count and PTT (PTT can sometimes be mildly elevated). Although vitamin K deficiency is common in newborns, it is very uncommon in otherwise healthy children and adults. In addition, the family history of bleeding disorder makes this much less likely than vWD.

(Choice E) Patients with severe liver disease often have impaired hepatic synthetic function and are unable to generate sufficient quantities of clotting factors. Therefore, they often have elevated PT and PTT (with normal or low platelets). This otherwise healthy boy is unlikely to have significant liver disease.

Educational objective:
Von Willebrand disease is the most common inherited bleeding disorder and is usually transmitted in an autosomal dominant fashion. Symptomatic patients typically present with easy bruising and mucosal bleeding. Laboratory evaluation will show normal platelets, normal PT, and either normal or prolonged PTT due to low levels of factor VIII.

Pathophysiology	Hematology & Oncology	Von willebrand disease
Subject	System	Topic

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A 42-year-old Caucasian male undergoes lymph node biopsy for persistent cervical lymphadenopathy. Histologic examination reveals a population of small lymphocytes arranged in a follicular pattern. The lymphocytes also demonstrate overexpression of the *bcl-2* gene, which normally inhibits which of the following?

A. Cytoplasmic receptor activation (3%)
B. Ras-induced signal transmission (8%)
C. Nuclear transcription (10%)
D. DNA mismatch accumulation (3%)
✓ E. Cell death cascade (74%)

Correct
74% Answered correctly
03 mins Time Spent
01/30/2021 Last Updated

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As a B-cell neoplasm, follicular lymphoma contains tumor cells that express pan B-cell antigens (CD19, CD20, and CD79a), CD21, and CD10. The characteristic cytogenetic abnormality associated with follicular lymphoma is a translocation of the *bcl-2* oncogene from chromosome 18 to the Ig heavy chain locus on chromosome 14 [t(14;18)]. Juxtaposition of the *bcl-2* gene with the Ig heavy chain region results in overexpression of the Bcl-2 protein product. Bcl-2 protein inhibits apoptosis of tumor cells, thereby facilitating neoplastic growth.

(Choices A and C) The *bcl-2* gene does not affect cytoplasmic receptor activation or nuclear transcription.

(Choice B) Ras protein is a component of the MAP-kinase pathway, a signaling system that transmits stimuli from the cell surface receptor to the nucleus. Ras overexpression renders cells more sensitive to mitogenic stimuli. This mutation occurs in pancreatic, gallbladder, colon, endometrial, thyroid, and lung cancers.

(Choice D) Mutations of genes responsible for DNA mismatch repair lead to hereditary nonpolyposis colon cancer (Lynch syndrome). This condition is characterized by a familial predisposition to colon cancer and other visceral malignancies.

Educational Objective:

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(Choice B) Ras protein is a component of the MAP-kinase pathway, a signaling system that transmits stimuli from the cell surface receptor to the nucleus. Ras overexpression renders cells more sensitive to mitogenic stimuli. This mutation occurs in pancreatic, gallbladder, colon, endometrial, thyroid, and lung cancers.

(Choice D) Mutations of genes responsible for DNA mismatch repair lead to hereditary nonpolyposis colon cancer (Lynch syndrome). This condition is characterized by a familial predisposition to colon cancer and other visceral malignancies.

Educational Objective:

Overexpression of *bcl-2* leads to increased secretion of Bcl-2 protein, which inhibits apoptosis and promotes survival of tumor cells. This overexpression occurs in follicular lymphoma secondary to translocation of the *bcl-2* oncogene from chromosome 18 to the Ig heavy chain locus on chromosome 14 [t(14;18)].

Pathology	Hematology & Oncology	Nonhodgkin lymphoma
Subject	System	Topic

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A 54-year-old previously healthy man comes to the clinic after 2 months of progressive, generalized weakness and easy fatigability. He also has abdominal discomfort and early satiety. The patient works as a security advisor and has not traveled recently. He is afebrile and other vitals signs are normal. On examination, he has pallor, abdominal distension, and massive splenomegaly with the spleen tip crossing the midline. No peripheral lymphadenopathy is present. Peripheral blood cell count shows pancytopenia. Bone marrow aspiration is attempted, but no marrow can be aspirated. Which of the following findings is most likely to be seen in this patient?

- A. Intraerythrocytic ring forms (6%)
- B. Lymphocytes with cytoplasmic projections (46%)
- C. Myeloid cells with azurophilic rodlike granules (25%)
- D. ~~Positive heterophile antibodies~~ (10%)
- E. ~~Ringed sideroblasts~~ (10%)

Incorrect

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Lymphocytes with cytoplasmic projections are seen in **hairy cell leukemia**, an indolent B-cell neoplasm (predominantly diagnosed in **middle-aged men**) that infiltrates the bone marrow and reticuloendothelial system. Bone marrow infiltration and cytokine production cause **fibrosis** and bone marrow failure, resulting in **pancytopenia**. A bone marrow aspirate is usually unsuccessful (**"dry tap"**). Splenic red pulp infiltration can result in **massive splenomegaly** (ie, crossing midline or extending into left lower quadrant). Common manifestations include left upper quadrant pain, fatigue, weakness, fever, and recurrent infections. The diagnosis is made by bone marrow biopsy and **flow cytometry**, which has replaced tartrate-resistant acid phosphatase (**TRAP**) activity testing.

(Choice A) Intraerythrocyte ring forms are seen in malaria. This patient has no travel history and no fevers to suggest malaria.

(Choice C) Myeloid cells with azurophilic rodlike granules (Auer rods) can be found in acute myeloid leukemias, which do not typically cause hepatosplenomegaly.

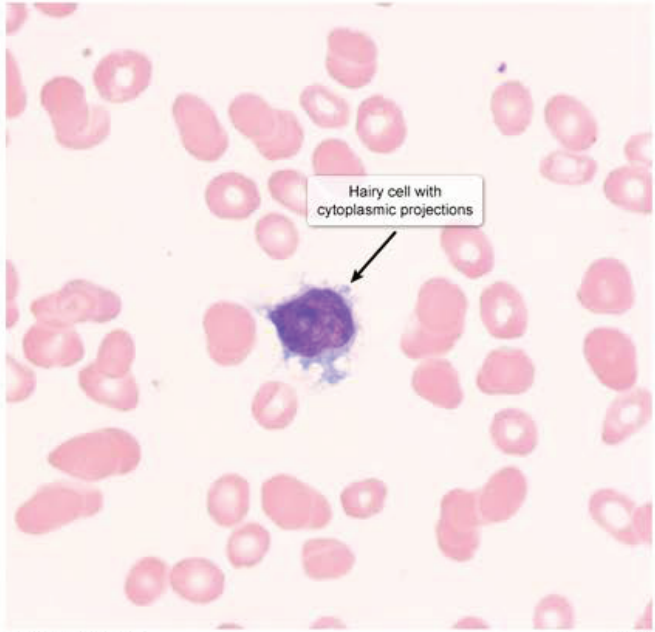
(Choice D) Heterophile antibodies are found in most patients with Epstein-Barr virus-induced infectious mononucleosis, which commonly presents in young adults with low-grade fever, pharyngitis, and cervical lymphadenopathy. Mild hepatosplenomegaly may be present.

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Exhibit Display

Hairy cell leukemia*



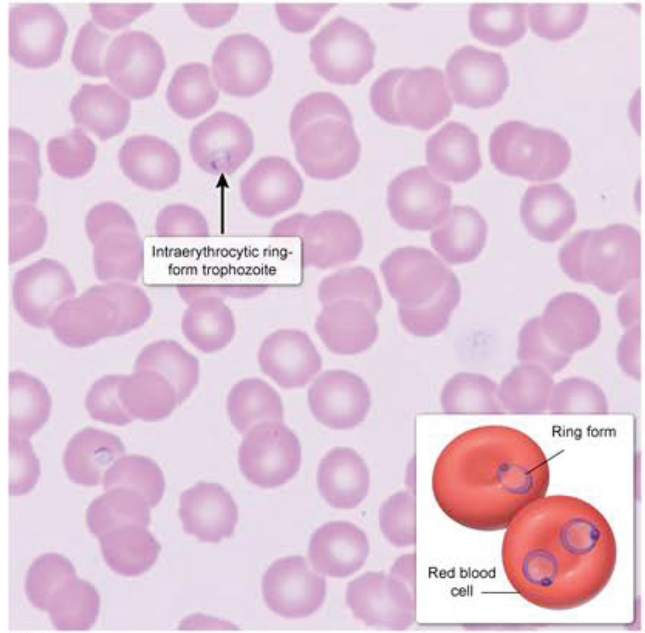
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Exhibit Display

Plasmodium falciparum



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fevers to suggest malaria.

(Choice C) Myeloid cells with azurophilic rodlike granules (Auer rods) can be found in acute myeloid leukemias, which do not typically cause hepatosplenomegaly.

(Choice D) Heterophile antibodies are found in most patients with Epstein-Barr virus-induced infectious mononucleosis, which commonly presents in young adults with low-grade fever, pharyngitis, and cervical lymphadenopathy. Mild hepatosplenomegaly may be present.

(Choice E) Ringed sideroblasts are abnormal erythrocyte precursors found in myelodysplastic syndrome (MDS) and characterized by mitochondrial iron accumulation surrounding the nucleus. Patients with MDS typically have petechiae, weakness, and recurrent infections; splenomegaly is uncommon.

Educational objective:
Hairy cell leukemia is an indolent B-cell neoplasm predominantly found in middle-aged men and characterized by bone marrow failure and infiltration into the reticuloendothelial system, causing massive splenomegaly. Other typical features include a "dry tap" (unsuccessful bone marrow aspiration) and the presence of lymphocytes with cytoplasmic projections.

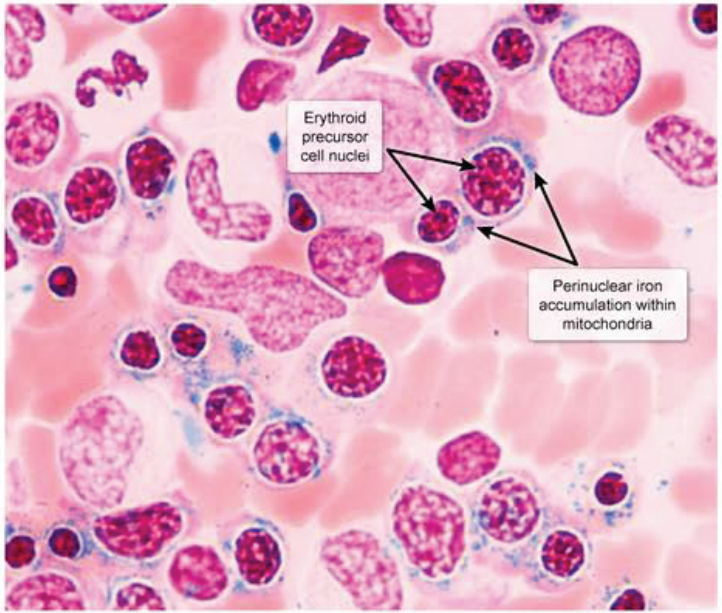
References

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Exhibit Display

Ring sideroblasts



Bone marrow aspirate – Prussian blue stain

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A 66-year-old man comes to the office due to several weeks of back and lower extremity pain. The pain feels dull and achy and is worsened by movement, causing him to have difficulty bearing weight and ambulating. He has had no bladder or bowel dysfunction, extremity weakness, or numbness. The patient takes metformin for type 2 diabetes mellitus. He drinks 2 alcoholic beverages daily. Physical examination shows no gross abnormality or deformity of the back or extremities. There is no swelling or redness of the legs, and neurological examination is normal. A radiograph of the right lower extremity is shown in the exhibit. Laboratory results are as follows:

Hemoglobin	9.6 g/dL
Mean corpuscular volume	92/μm^3
Creatinine	1.6 mg/dL
Calcium	11.0 mg/dL
Glucose	220 mg/dL
Total protein	8.8 g/dL
Albumin	3.8 g/dL

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Total protein	8.8 g/dL
Albumin	3.8 g/dL

Which of the following is the most likely explanation for this patient's bone changes?

A. Decreased urinary calcium excretion (4%)
B. Increased 1,25-dihydroxyvitamin D production (2%)
C. Increased secretion of parathyroid hormone (27%)
D. Local tumor cell–mediated activation of osteoblasts (7%)
E. Local tumor cell–mediated activation of osteoclasts (58%)

Correct

58% Answered correctly

02 mins, 10 secs Time Spent

09/05/2020 Last Updated

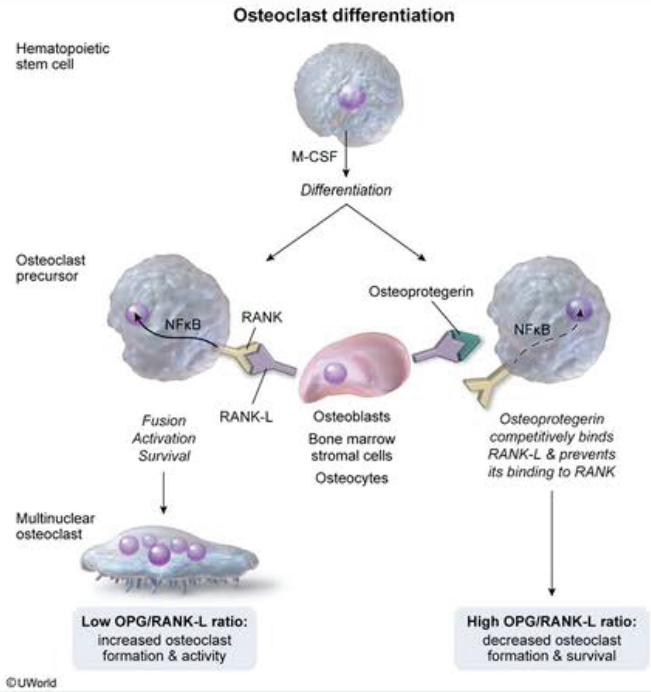
Explanation

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Explanation

Exhibit Display



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its binding to RANK

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formation & activity

formation & survival

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This patient with mild renal insufficiency, normocytic anemia, hypercalcemia, and bone pain has the classic manifestations of **multiple myeloma** (MM), a plasma cell malignancy associated with excessive production of monoclonal immunoglobulin (paraprotein). Myeloma cells replicate in the bone marrow and release cytokines that stimulate osteoclasts and inhibit osteoblasts, which leads to the generation of purely osteolytic (radiolucent) bone lesions.

Bone remodeling is tightly regulated by osteocytes (stromal bone marrow cells that are embedded within the lacuna-canalicular network) in conjunction with signals from the bone marrow and the bone surface. The RANK/RANKL pathway plays a prominent role. RANK is a transmembrane receptor on the surface of osteoclast precursors, which is activated by RANK-ligand (RANKL) produced by osteocytes. **Activation of RANK** leads to the differentiation of osteoclast precursors into mature osteoclasts.

Myeloma cells stimulate osteoclast maturation by producing RANKL and by destroying OPG (mediated by a secreted proteoglycan). They also uniquely inhibit osteoblast activity by secreting cytokines that block osteoblast function (eg, IL-3, IL-7, Wnt pathway inhibitors). This tilts the balance of bone remodeling strongly toward **osteolytic bone destruction**, which results in many of the characteristic findings seen in MM, including bone pain, **hypercalcemia** (liberation of calcium during osteolysis), and purely radiolucent

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formation & activity ... formation & survival

Exhibit Display

Multiple myeloma skeletal survey



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MM, including bone pain, **hypercalcemia** (liberation of calcium during osteolysis), and purely radiolucent

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MM, including bone pain, **hypercalcemia** (liberation of calcium during osteolysis), and purely radiolucent (osteolytic) bone lesions.

(Choice A) Decreased urinary calcium excretion can be seen with thiazide diuretic use and can result in hypercalcemia. However, this effect is associated with an increase in bone density; radiolucent bone lesions would not be seen.

(Choices B and C) 1,25 dihydroxyvitamin D and parathyroid hormone break down bone by increasing RANKL and decreasing OPG expression. Although vitamin D toxicosis and hyperparathyroidism can be associated with hypercalcemia, they are not associated with anemia or elevations in total serum protein.

(Choice D) Several tumors that spread to the bones stimulate osteoclasts, but only myeloma cells also inhibit osteoblasts. Therefore, myeloma cells are one of the few tumors to cause purely osteolytic (radiolucent) lesions. Most other tumors have at least some areas of sclerosis (osteoblastic activity).

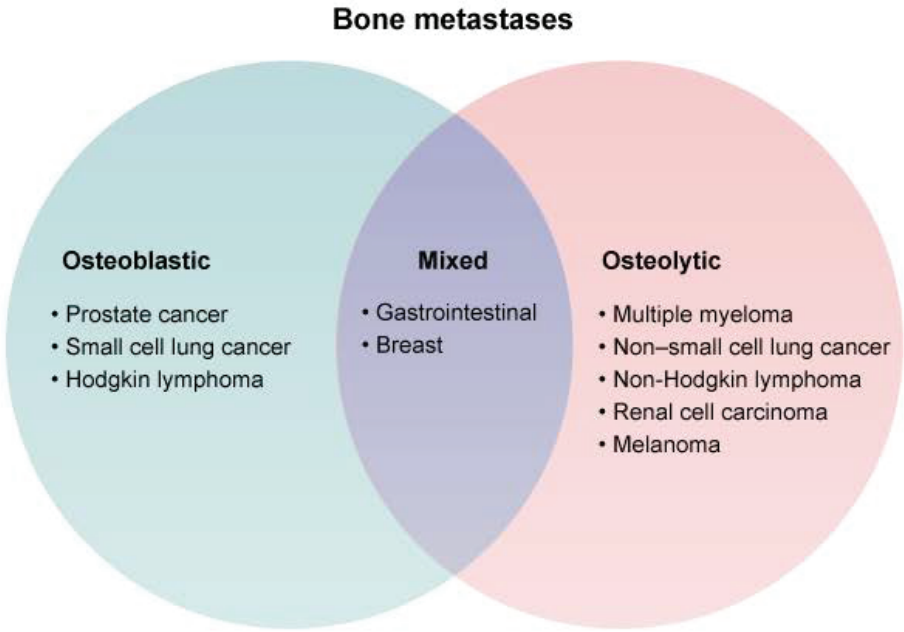
Educational objective:
Multiple myeloma is a plasma cell malignancy associated with purely radiolucent (osteolytic) bone lesions due to the stimulation of osteoclasts and the inhibition of osteoblasts. Myeloma cells stimulate osteoclast development by secreting RANK-ligand and destroying osteoprotegerin, which increases RANK activity and results in osteoclast differentiation.

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MM, including bone pain, **hypercalcemia** (liberation of calcium during osteolysis), and purely radiolucent

Exhibit Display



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A 28-year-old man comes to the emergency department due to anxiety, weakness, dyspnea, and headaches. He is a graduate student in chemistry and was accidentally exposed to nitrites in his research laboratory. Physical examination is notable for cyanosis that is not improved by administration of supplemental oxygen via facemask. Analysis of a sample of arterial blood drawn from this patient prior to any oxygen supplementation is most likely to reveal normal values for which of the following?

A. ~~Bound fraction of oxygen in the arterial blood~~ (6%)
B. ~~Oxygen carrying capacity of the arterial blood~~ (16%)
C. Oxygen content of the arterial blood (15%)
D. ~~Oxygen delivery to peripheral tissues~~ (2%)
E. Partial pressure of oxygen in the arterial blood (59%)

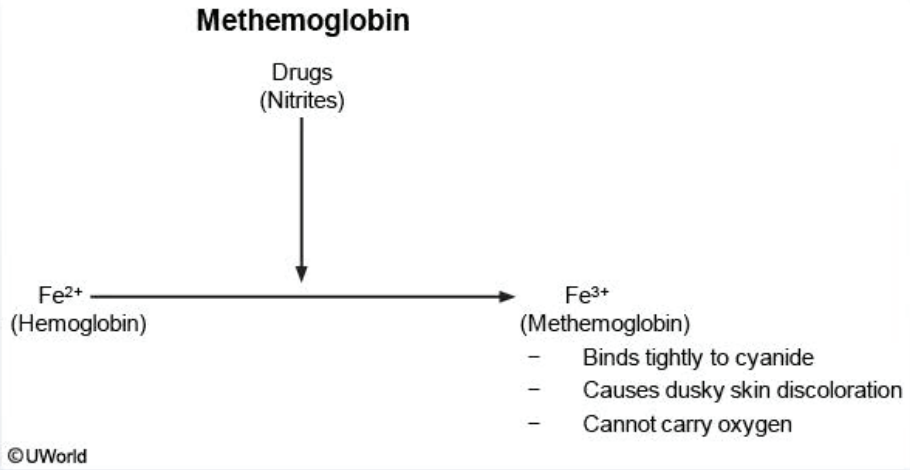
Incorrect
Correct answer
E

59%
Answered correctly

02 mins, 48 secs
Time Spent

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Iron bound to heme is normally in the **reduced** ferrous (Fe^{2+}) state. **Nitrites** cause poisoning by inducing the conversion of this heme iron to the **oxidized** ferric (Fe^{3+}) state, leading to the formation of **methemoglobin**. With iron in the oxidized ferric state, methemoglobin is unable to bind oxygen. In addition, the affinity of any residual ferrous iron in the hemoglobin tetramer is increased, causing a leftward shift of the oxygen-dissociation curve. However, the **partial pressure of oxygen** in blood, which represents the amount of oxygen dissolved in the plasma, is **unchanged**.

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represents the amount of oxygen dissolved in the plasma, is **unchanged**.

Methemoglobinemia causes **dusky** discoloration of the skin (similar to cyanosis), and because methemoglobin is unable to carry oxygen, a state of functional anemia is induced.

	PO_2 (dissolved oxygen)	**% Saturation of Hb**	**Total O_2 content** (both dissolved & O_2 attached to Hb)
CO poisoning	Normal	Decreased (CO competes with O_2)	Decreased
Anemia (low Hb)	Normal	Normal	Decreased
Polycythemia (high Hb)	Normal	Normal	Increased

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(Choices A, B, C, and D) Methemoglobin cannot bind to oxygen and therefore the oxygen content and oxygen carrying capacity of the arterial blood will decrease. The bound fraction of oxygen and oxygen delivery to the peripheral tissues will also decrease due to methemoglobin's inability to carry and deliver

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(low Hb)	Normal	Normal	Decreased
Polycythemia (high Hb)	Normal	Normal	Increased

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(Choices A, B, C, and D) Methemoglobin cannot bind to oxygen and therefore the oxygen content and oxygen carrying capacity of the arterial blood will decrease. The bound fraction of oxygen and oxygen delivery to the peripheral tissues will also decrease due to methemoglobin's inability to carry and deliver oxygen.

Educational objective:

Methemoglobinemia causes dusky discoloration of the skin (similar to cyanosis), and because methemoglobin is unable to carry oxygen, a state of functional anemia is induced. However, the blood partial pressure of oxygen will be unchanged as it is a measure of oxygen dissolved in plasma and is unrelated to hemoglobin function.

Biochemistry	Hematology & Oncology	Methemoglobinemia
Subject	System	Topic

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A 29-year-old woman comes to the emergency department due to fever and headache for the last week. The patient has a generalized tonic-clonic seizure while being evaluated. Laboratory results are as follows:

Hemoglobin	6.1 g/dL
Platelets	16,000/mm^3
Creatinine	2.2 mg/dL
Total bilirubin	4.3 mg/dL
Serum haptoglobin	undetectable
PT	11 sec (INR 1.1)
Activated PTT	30 sec

Peripheral blood smear is shown in the exhibit. Which of the following is the most likely underlying cause of this patient's current condition?

A. Bacterial product–mediated overactivation of coagulation cascade (24%)

B. Decreased activity of von Willebrand factor–cleaving protease (49%)

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Exhibit Display



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B. Decreased activity of von Willebrand factor–cleaving protease (49%)

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Creatinine	2.2 mg/dL
Total bilirubin	4.3 mg/dL
Serum haptoglobin	undetectable
PT	11 sec (INR 1.1)
Activated PTT	30 sec

Peripheral blood smear is shown in the exhibit. Which of the following is the most likely underlying cause of this patient's current condition?

A. Bacterial product–mediated overactivation of coagulation cascade (24%)

B. Decreased activity of von Willebrand factor–cleaving protease (49%)

C. Expansion of neoplastic myeloid precursor cells in bone marrow (5%)

D. Inherited deficiency of glucose-6-phosphate dehydrogenase enzyme (15%)

E. Missense mutation at the sixth position of the hemoglobin beta chain (5%)

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Thrombotic thrombocytopenic purpura	
Pathophysiology	• ↓ ADAMTS-13 level → uncleaved vWF multimers → platelet trapping & activation • Acquired (autoantibody) or hereditary
Clinical features	• Hemolytic anemia (↑ LDH, ↓ haptoglobin) with schistocytes on peripheral smear • Thrombocytopenia (↑ bleeding time, normal PT/PTT) • Sometimes with: ◦ Renal failure ◦ Neurologic manifestations ◦ Fever

LDH = lactate dehydrogenase; **vWF** = von Willebrand factor.

This patient has the classic **pentad** of manifestations for acquired **thrombotic thrombocytopenic**

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This patient has the classic **pentad** of manifestations for acquired **thrombotic thrombocytopenic purpura** (TTP):

- **Severe thrombocytopenia**: Platelet-rich clots form in the microvasculature, leading to rapid platelet consumption.
- **Microangiopathic hemolytic anemia** (MAHA): Erythrocytes are mechanically sheared by the microvascular thrombi, leading to intravascular hemolytic anemia. This typically causes an **elevated indirect bilirubin** level and an **undetectable haptoglobin** level (haptoglobin binds free hemoglobin in the circulation), but confirmation of MAHA requires identification of schistocytes (eg, triangle cells, helmet cells) on peripheral blood smear.
- **Neurologic manifestations** (eg, headache, seizure), **renal insufficiency**, and **fever** (the remainder of the pentad) occur in a minority of patients

Unlike patients who have disseminated intravascular coagulation (a consumptive coagulopathy also associated with MAHA and thrombocytopenia), those with TTP have **normal coagulation studies** because coagulation factors are not significantly consumed by the formation of platelet-rich clots **(Choice A)**.

TTP is triggered by the formation of autoantibody inhibitors against **ADAMTS-13**, a protease that **cleaves**

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TTP is triggered by the formation of autoantibody inhibitors against **ADAMTS-13**, a protease that **cleaves ultralarge von Willebrand factor** (VWF) multimers in the circulation, reducing their prothrombotic activity. Patients with TTP have very low levels of ADAMTS-13, which increases the proportion of ultralarge VWF multimers and leads to the aggregation and activation of platelets. **Plasma exchange**, which removes the autoantibody inhibitors against ADAMTS-13, is generally curative.

(Choice C) Expansion of neoplastic myeloid precursors in the bone marrow is seen in acute myeloid leukemia, which can cause anemia and thrombocytopenia due to bone marrow infiltration. However, peripheral blood smear would show leukemic blast cells, not schistocytes.

(Choice D) Inherited deficiency of glucose-6-phosphate dehydrogenase typically causes hemolytic anemia during times of oxidative stress (eg, infection, medication exposure, certain foods). High bilirubin and low haptoglobin are often present due to hemolytic anemia; however, thrombocytopenia is not seen, and peripheral smear would show bite cells and Heinz bodies, not schistocytes.

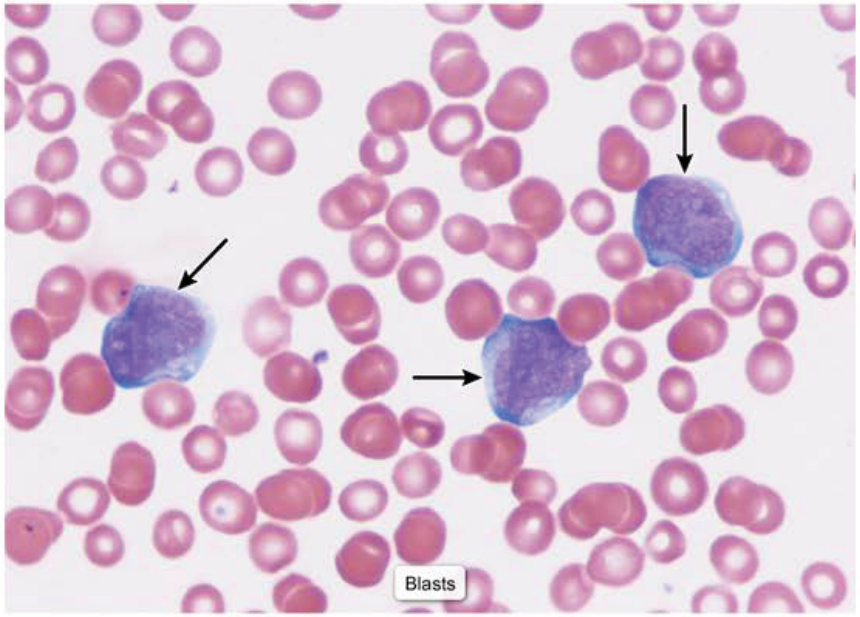
(Choice E) A missense mutation at the sixth position of the hemoglobin beta chain is seen in sickle cell anemia, which is marked by periods of acute on chronic hemolytic anemia (eg, elevated bilirubin, low haptoglobin). However, peripheral smear would show sickled erythrocytes, not schistocytes; in addition, thrombocytopenia is not generally seen.

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Exhibit Display

Acute myeloid leukemia



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haptoglobin are often present due to hemolytic anemia; however, thrombocytopenia is not seen, and peripheral smear would show bite cells and Heinz bodies, not schistocytes.

(Choice E) A missense mutation at the sixth position of the hemoglobin beta chain is seen in sickle cell anemia, which is marked by periods of acute on chronic hemolytic anemia (eg, elevated bilirubin, low haptoglobin). However, peripheral smear would show sickled erythrocytes, not schistocytes; in addition, thrombocytopenia is not generally seen.

Educational objective:

Thrombotic thrombocytopenic purpura classically presents with the pentad of severe thrombocytopenia, microangiopathic hemolytic anemia (eg, schistocytes on peripheral smear), renal insufficiency, neurologic symptoms, and fever. However, all these signs and symptoms are rarely present. Diagnosis is often made by identifying severe deficiency of ADAMTS-13, a protease that cleaves large von Willebrand factor multimers off the endothelium.

Pathology	Hematology & Oncology	Thrombotic thrombocytopenic purpura
Subject	System	Topic

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A 24-year-old woman, gravida 1 para 0, at 14 weeks gestation, comes to the emergency department due to left leg swelling and pain for the past 2 days. She has had no chest pain or shortness of breath. The patient has no prior medical conditions and her only medication is a prenatal vitamin. She is a lifetime nonsmoker. Physical examination shows 1+ edema of the left lower extremity to the knee, associated with mild erythema. The left calf diameter measures 3 cm greater than the right. Doppler ultrasonography shows left popliteal and femoral vein thrombosis. Serum creatinine level is 0.7 mg/dL. Which of the following is the most appropriate pharmacotherapy for this patient?

A. Apixaban (3%)
B. Clopidogrel (4%)
C. Dabigatran (4%)
D. Enoxaparin (64%)
E. Low-dose aspirin (3%)
F. Tissue plasminogen activator (15%)
G. Warfarin (3%)

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Explanation

Pregnancy increases the risk of **venous thromboembolism** (VTE) due to anatomic changes (eg, uterine compression of the inferior vena cava and iliac veins) and physiologic hypercoagulability (eg, increased production of clotting factors, decreased protein S levels, protein C resistance). **Heparins** are ideal anticoagulants for most pregnant women as they do not cross the placenta and the risk of fetal bleeding and teratogenicity is low:

- **Low-molecular-weight heparin (LMWH)** (eg, enoxaparin, dalteparin) is preferred as it has a relatively long half-life (4.5 hours) and does not require routine laboratory monitoring. However, it is renally cleared and cannot be used in patients with severe renal insufficiency (creatinine clearance <30 mL/min).
- Unfractionated heparin has a short half-life (1-2 hours) and requires frequent lab draws (ie, PTT) due to its more varied anticoagulant effect. However, it may be used in patients with renal insufficiency. It is also used in place of LMWH at term (37 weeks gestation) as it can be discontinued at the onset of labor to minimize hemorrhagic risk.

(Choices A and C) Direct thrombin inhibitors (eg, dabigatran) and factor Xa inhibitors (eg, apixaban) are not recommended in pregnant women. Both have been associated with fetal toxicity in animal studies.

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not recommended in pregnant women. Both have been associated with fetal toxicity in animal studies.

(Choices B and E) Clopidogrel and aspirin have no role in acute VTE treatment. Clopidogrel, which blocks the platelet adenosine diphosphate receptor and limits platelet aggregation, is used in treatment of coronary artery disease, acute coronary syndrome, and prevention of recurrent ischemic stroke. Low-dose aspirin is prescribed to certain pregnant patients at risk of preeclampsia.

(Choice F) Recombinant tissue plasminogen activator is used for clot lysis. It has a high risk of major bleeding and is typically reserved for those with massive deep vein thrombosis at risk of limb ischemia or life-threatening pulmonary embolism with hypotension. Anticoagulation alone is preferred for VTE in hemodynamically stable patients.

(Choice G) Warfarin crosses the placenta, increasing risks of teratogenicity and fetal hemorrhage, and is typically avoided in pregnancy.

Educational objective:
Heparins are ideal anticoagulants for most patients with thromboembolic disease in pregnancy as they do not cross the placenta and therefore the risk of fetal bleeding or teratogenicity is low. Low molecular weight heparin (eg, enoxaparin) is the preferred therapy, with patients transitioned to unfractionated heparin at term.

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A 24-year-old man comes to the oncology clinic for a follow-up visit. The patient was diagnosed with Hodgkin lymphoma 4 months ago and received combination chemotherapy. He has had a nonproductive cough and shortness of breath with exertion over the past 2 weeks. On examination, there is no jugular venous distension or pedal edema. Heart sounds are normal with no murmurs. Lung auscultation reveals bilateral fine inspiratory crackles. Chest radiograph shows bilateral reticular interstitial opacities. Pulmonary function testing shows a restrictive pattern with decreased diffusion capacity for carbon monoxide. Chest x-ray and pulmonary function testing prior to the initiation of chemotherapy were normal. Which of the following is the most likely mechanism of action of the medication causing this patient's current symptoms?

A. Disrupts microtubule polymerization causing M-phase arrest (6%)
B. Impairs DNA synthesis by inhibiting thymidylate synthase (9%)
C. Induces free radical formation and DNA strand breaks (72%)
D. Inhibits topoisomerase II leading to DNA strand breaks (4%)
E. Inhibits tyrosine kinases and cellular replication (3%)

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Specific toxicities of common chemotherapeutic agents

Chemotherapy agent	Mechanism of Action	Toxicity
Anthracyclines (eg, doxorubicin)	• Binds with topoisomerase II to cleave DNA • Binds with iron to generate free radicals	• Dilated cardiomyopathy
Bleomycin	• Induces free radical formation	• Pulmonary fibrosis
Cisplatin	• Cross-links DNA to inhibit DNA synthesis	• Nephrotoxicity • Ototoxicity • Peripheral neuropathy
Cyclophosphamide	• Cross-links DNA to inhibit DNA synthesis	• Hemorrhagic cystitis • Bladder cancer
Paclitaxel	• Inhibits microtubule disassembly	• Neuropathy
Vincristine/ vinblastine	• Binds beta-tubulin to inhibit microtubule formation	• Neuropathy

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vinblastine	formation

Bleomycin is commonly used in the treatment of Hodgkin lymphoma and germ cell tumors; it exerts an antineoplastic effect by binding with iron and oxygen molecules to create **free radicals** that cause **DNA strand breaks**. Lung toxicity, usually in the form of **pulmonary fibrosis**, is the most clinically important adverse effect of the drug.

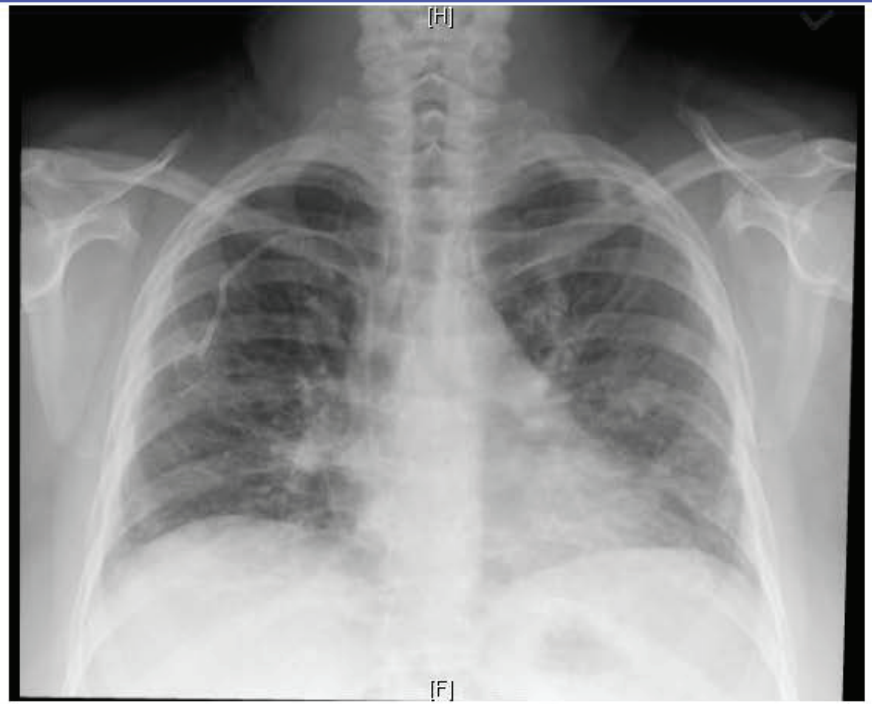
Toxicity from bleomycin likely results from oxidative free-radical damage to healthy tissue, leading to a cycle of tissue damage and repair. The lungs are particularly susceptible because they lack bleomycin hydrolase, an enzyme that helps inactivate bleomycin in other tissues. Patients who develop lung toxicity typically experience **dyspnea**, **nonproductive cough**, and crackles on lung auscultation within 6 months following initiation of therapy. Bibasilar interstitial opacities are typically seen on chest x-ray, and spirometry demonstrates reduced FVC with relatively preserved FEV1, consistent with a **restrictive pattern**. In addition, there is **reduced diffusion capacity for carbon monoxide (DLCO)** due to impaired gas exchange across an inflamed or fibrosed interstitium.

(Choice A) Vinka alkaloids (eg, vincristine, vinblastine) bind to beta-tubulin to disrupt microtubule polymerization and prevent mitotic cell division. Peripheral neuropathy is a common adverse effect of these drugs.

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vinblastine formation

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(eg, anemia, neutropenia) can occur.

(Choice D) Etoposide inhibits topoisomerase II to cause DNA strand breaks, and is commonly associated with bone marrow suppression. Anthracyclines (eg, doxorubicin) also exert at least part of their antineoplastic effect by binding to topoisomerase II and can cause cardiotoxicity that manifests as dilated cardiomyopathy.

(Choice E) The tyrosine kinase inhibitors imatinib and erlotinib are used to treat chronic myelogenous leukemia and lung cancer, respectively. These drugs disrupt cellular replication and commonly cause diarrhea and skin rash.

(Choice F) Proteasome inhibitors (eg, bortezomib) are used in the treatment of multiple myeloma. These drugs can cause bone marrow suppression and sometimes peripheral neuropathy.

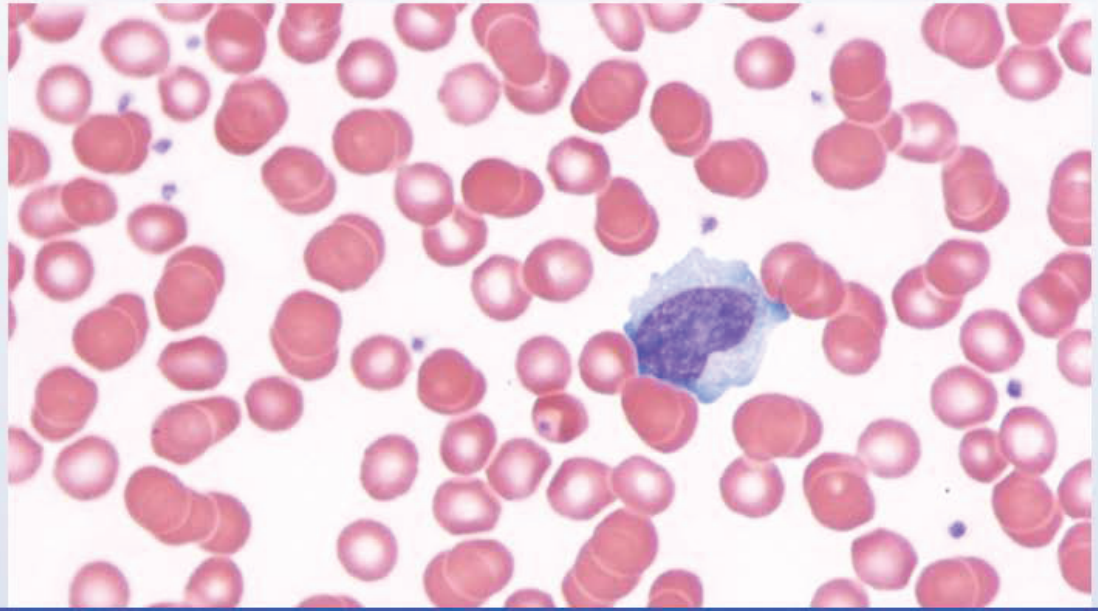
Educational objective:
Bleomycin is an antineoplastic agent that binds to iron and oxygen molecules to create free radicals that cause DNA strand breaks. The most clinically important adverse effect of bleomycin is lung toxicity, usually manifesting as pulmonary fibrosis. Patients develop dyspnea and nonproductive cough, and pulmonary function testing shows a restrictive pattern with reduced diffusion capacity for carbon monoxide (DLCO).

References

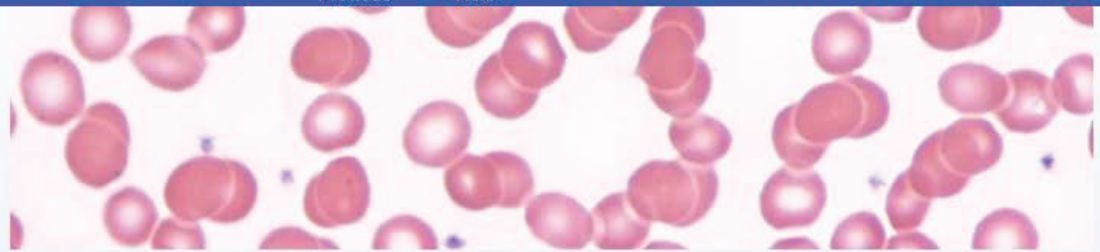
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A 16-year-old previously healthy boy is brought to the office due to fever, malaise, and sore throat. The patient says that he gets tired even by simply getting out of bed. Physical examination shows palatal petechiae, cervical lymphadenopathy, and splenomegaly. His peripheral blood smear is shown in the image below.



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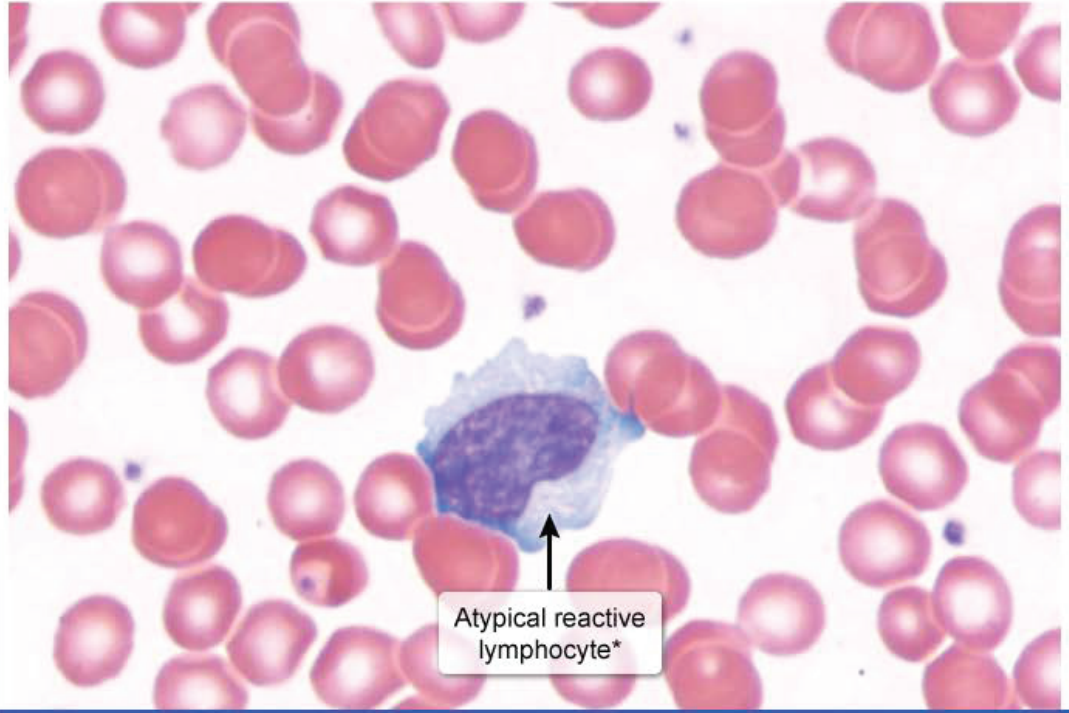
Horse erythrocytes agglutinate when exposed to the patient's serum. The agent causing this patient's disease is most strongly associated with which of the following malignancies?

A. Acute myeloid leukemia (8%)
B. Cervical carcinoma (0%)
C. Hepatocellular carcinoma (0%)
D. Kaposi sarcoma (3%)
E. Mucosa-associated lymphoid tissue tumor (4%)
F. Multiple myeloma (9%)
G. Nasopharyngeal carcinoma (72%)

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Epstein-Barr virus infection



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*Large lymphocyte with abundant blue cytoplasm often indented by adjacent erythrocytes

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Sore throat, moderate to high fever, palatal petechiae, **lymphadenopathy** (commonly posterior cervical or auricular), splenomegaly, and **atypical** (reactive) **lymphocytosis** are classic signs and symptoms of **infectious mononucleosis**, a disease common among teenagers and young adults. Ninety percent of cases of infectious mononucleosis are caused by the **Epstein-Barr virus** (EBV); however, cytomegalovirus, HIV, and *Toxoplasma* are some of the other agents known to cause non-EBV infectious mononucleosis. EBV infection induces **heterophile antibodies**, which react to antigens from animal erythrocytes (sheep in the Paul-Bunnell test and horse in the Monospot test). The heterophile antibody tests are sensitive and specific for EBV-associated infectious mononucleosis.

EBV replicates primarily in B lymphocytes and is also associated with **malignancies**, including **Burkitt lymphoma** (especially the endemic African type) and **nasopharyngeal carcinoma**. Many disorders in immunocompromised patients are caused by EBV, including central nervous system lymphoma in HIV-positive patients and post-transplant lymphoproliferative disorder (PTLD) in allograft recipients.

(Choices A and F) There is no classic association between acute myeloid leukemia or multiple myeloma and viral infection.

(Choice B) Cervical carcinoma is strongly associated with human papillomavirus (types 16, 18, 31, and

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positive patients and post-transplant lymphoproliferative disorder (PTLD) in allograft recipients.

(Choices A and F) There is no classic association between acute myeloid leukemia or multiple myeloma and viral infection.

(Choice B) Cervical carcinoma is strongly associated with human papillomavirus (types 16, 18, 31, and 33) infection.

(Choice C) Chronic infection with either hepatitis B or C virus significantly increases the risk of hepatocellular carcinoma.

(Choice D) Kaposi sarcoma is strongly associated with HIV and human herpes virus type 8 infections.

(Choice E) Gastric adenocarcinoma and mucosa-associated lymphoid tissue tumor (MALToma) are associated with *Helicobacter pylori* infection.

Educational objective:
Epstein-Barr virus causes infectious mononucleosis in teenagers and young adults. It is also associated with a number of malignant conditions, including Burkitt lymphoma and nasopharyngeal carcinoma.

Pathology Hematology & Oncology Infectious mononucleosis

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A 62-year-old woman comes to the office with severe fatigue and progressive exertional dyspnea for the past 6 months. She reports several episodes of food getting stuck in her throat, especially when attempting to swallow large chunks of solid food. On physical examination, she has mucosal pallor and her tongue appears smooth and red. Additional findings are shown below.



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Supplementation with which of the following is most likely to improve this patient's condition?

A. Erythropoietin (2%)

B. Filgrastim (1%)

C. Folic acid (3%)

✓ D. Iron (78%)

E. Pyridoxine (5%)

F. Vitamin B_{12} (5%)

G. Vitamin C (3%)

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Explanation

Plummer-Vinson syndrome (PVS) is a rare disease characterized by **dysphagia and iron deficiency anemia**. Patients develop weakness, fatigue, and dyspnea secondary to the anemia; dysphagia develops due to **esophageal web** formation. Other physical examination findings associated with iron deficiency include **koilonychia** (spoon-shaped nails) and a **shiny red tongue** secondary to atrophy of lingual papillae. PVS is treated with **iron supplementation**, which resolves the symptoms related to iron-deficiency anemia and often improves the dysphagia.

(Choice A) Erythropoietin is used to treat anemia associated with chronic renal failure and chemotherapy.

(Choice B) Filgrastim is a granulocyte colony-stimulating factor analog used to treat neutropenia in patients following chemotherapy or bone marrow transplant.

(Choices C and F) Deficiency of vitamin B_{12} or folic acid results in megaloblastic anemia. This patient's presentation is more specific for iron deficiency, which causes microcytic anemia.

(Choice E) Pyridoxine (vitamin B_6) is required as a cofactor for the first step in heme synthesis. Deficiency causes sideroblastic anemia, neurologic deficits, and dermatitis.

(Choice G) Vitamin C is sometimes added to improve oral absorption of non-heme iron, but would be

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presentation is more specific for iron deficiency, which causes microcytic anemia.

(Choice E) Pyridoxine (vitamin B_6) is required as a cofactor for the first step in heme synthesis. Deficiency causes sideroblastic anemia, neurologic deficits, and dermatitis.

(Choice G) Vitamin C is sometimes added to improve oral absorption of non-heme iron, but would be ineffective without concurrent iron supplementation.

Educational objective:
Plummer-Vinson syndrome is characterized by dysphagia (esophageal web formation) and iron deficiency anemia. Findings associated with iron deficiency include koilonychia (spoon-shaped nails) and a shiny red tongue. Most symptoms resolve following iron supplementation.

References

- Plummer-Vinson syndrome.

Pathology	Hematology & Oncology	Iron deficiency anemia
Subject	System	Topic

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A 37-year-old man comes to the emergency department due to blood-tinged vomiting and abdominal discomfort. Six months ago, he lost his job as an investment banker and began drinking large amounts of whiskey on a daily basis. He has since been hospitalized several times with alcohol intoxication. His temperature is 36.7 C (98 F), blood pressure is 110/70 mm Hg, pulse is 84/min, and respirations are 18/min. Physical examination shows a firm, enlarged liver. Peripheral blood smear results show neutrophils with 6-8 nuclear lobes. Which of the following is the most likely explanation for this latter finding?

A. Blood lipid abnormality (1%)
B. Chronic blood loss (1%)
C. Cobalamin deficiency (22%)
D. Folate deficiency (71%)
E. Hypothyroidism (0%)
F. Myelodysplasia (2%)

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Alcoholism is one of the most common causes of **folate deficiency** anemia due to poor dietary intake and impaired folate absorption, utilization, and enterohepatic recycling. A normal individual with a folate-deficient diet can maintain normal red blood cell (RBC) production for months due to folate recycling, whereas a patient who consumes large amounts of alcohol will experience anemia within a few **weeks**. A reduced form of folic acid, tetrahydrofolic acid, is necessary for the synthesis of amino acids, thymidine, and purines. Impaired nucleotide synthesis leads to defective DNA production in blood cell precursors, resulting in abnormal cell division and **megaloblastic** hyperplasia of the bone marrow. The peripheral blood smear shows pancytopenia and hypersegmented neutrophils containing nuclei with >5 lobes. RBC abnormalities include ovalocytosis and **macrocytosis**, with a mean corpuscular volume (MCV) >100 μm^3.

(Choice A) Lipid abnormalities such as extreme hypertriglyceridemia can cause acute pancreatitis.

(Choice B) Chronic blood loss causes iron deficiency anemia, which is not characterized by hypersegmented neutrophils.

(Choice C) Vitamin B_{12} (cobalamin) deficiency is typically associated with pernicious anemia, gastrectomy, certain medications, and fish tapeworm infections. Chronic alcohol use can deplete vitamin B_{12} levels; however, given the body's large B_{12} stores, this depletion would take place over a period of many years not months. In addition, there is no mention in this patient of the neurologic symptoms that classically

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certain medications, and fish tapeworm infections. Chronic alcohol use can deplete vitamin B_{12} levels; however, given the body's large B_{12} stores, this depletion would take place over a period of many years not months. In addition, there is no mention in this patient of the neurologic symptoms that classically accompany B_{12} deficiency (eg, subacute combined degeneration with paresthesias, ataxia, and loss of proprioception).

(Choice E) Elevated MCV can be present in hypothyroidism, but hypersegmented neutrophils are classically not seen.

(Choice F) Myelodysplasia is a premalignant condition that manifests with pancytopenia, impaired blood cell differentiation, and clonal expansion of mutated hematopoietic cells in the bone marrow. Elevated MCV can be present, but hypersegmented neutrophils are not commonly seen.

Educational objective:

Folic acid deficiency anemia commonly occurs in alcoholism. It is a megaloblastic anemia that can develop within weeks. Peripheral blood smear shows macrocytosis, ovalocytosis, and neutrophils with hypersegmented nuclei.

References

- Disturbances of folic acid and homocysteine metabolism in alcohol abuse

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A 3-year-old boy comes to the emergency department for evaluation of oral bleeding that began 1 hour after a tooth extraction. The bleeding has persisted for approximately 30 minutes despite application of constant pressure with gauze. He has no significant past medical or surgical history. The patient takes no medications, and his vaccinations are up to date. Blood pressure is 90/60 mm Hg and pulse is 100/min. On physical examination, he has slow oozing of blood at the site of the dental extraction. Family history is significant for a maternal uncle who suffered from recurrent bleeding into his joints. Which of the following is most likely to be abnormal in this patient?

A. Haptoglobin level (0%)
B. ~~Hemoglobin level~~ (0%)
C. Partial thromboplastin time (80%)
D. ~~Platelet count~~ (3%)
E. Platelet function analyzer (3%)
F. ~~Prothrombin time~~ (8%)
G. ~~Thrombin time~~ (1%)

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Hemophilia A & B	
Inheritance	• X-linked recessive
Clinical features	• Delayed/prolonged bleeding after mild trauma ◦ Hemarthrosis, intramuscular hematomas ◦ Gastrointestinal or genitourinary tract bleeding ◦ Intracranial hemorrhage • Complications: hemophilic arthropathy
Laboratory findings	• ↑ Activated PTT • Normal platelet count & PT • Absent or ↓ factor VIII (hemophilia A) or factor IX (hemophilia B) activity
Treatment	• Factor replacement • Desmopressin for mild hemophilia A

Abnormal bleeding following tooth extractions or other surgical procedures can signify a quantitative or qualitative platelet defect, coagulopathy, or abnormal fibrinolysis. This patient's **male sex** and **family**

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Abnormal bleeding following tooth extractions or other surgical procedures can signify a quantitative or qualitative platelet defect, coagulopathy, or abnormal fibrinolysis. This patient's **male sex** and **family history** of **hemarthrosis** in a maternal male relative suggest an **X-linked coagulopathy** such as hemophilia A (factor VIII deficiency) or hemophilia B (factor IX deficiency, Christmas disease). Hemophilia A and B are indistinguishable clinically as both demonstrate similar symptoms and inheritance patterns. Both conditions are characterized by isolated prolongation of partial thromboplastin time due to defects in the intrinsic coagulation pathway. Prothrombin time [PT] and thrombin time [TT] are normal in patients with hemophilia.

When endothelial injury occurs, platelets are activated and form a hemostatic plug first, followed by activation of the coagulation cascade. Patients with hemophilia have normal platelet function and can form a platelet plug, so bleeding after procedures can be delayed rather than immediate, in contrast to patients with platelet disorders. Manifestations include **intramuscular hemorrhage**, hemarthrosis, and prolonged or **delayed bleeding** after surgical procedures.

(Choice A) Low haptoglobin is a sign of hemolytic anemia. Other associated findings include increased indirect bilirubin and lactate dehydrogenase.

(Choice B) This patient's hemoglobin level is likely normal since the oozing began recently and he has no

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(Choice B) This patient's hemoglobin level is likely normal since the oozing began recently and he has no history of chronic or recurrent bleeding.

(Choice D) Signs of thrombocytopenia include easy bruisability, petechiae, and mucocutaneous hemorrhage (eg, recurrent epistaxis, gingival hemorrhage). The absence of petechiae and the delayed bleeding onset make a platelet disorder unlikely.

(Choice E) The platelet function analyzer (PFA-100) test monitors the time needed for a patient's blood to form a platelet-based hemostatic plug in an in vitro environment. Abnormal results are seen in von Willebrand disease, inherited/acquired platelet dysfunction (eg, NSAID use), and thrombocytopenia.

(Choice F) PT reflects the extrinsic clotting pathway, which involves tissue factor, fibrinogen, and factors II, V, VII, and X. Vitamin K deficiency and warfarin anticoagulant therapy are common causes of isolated PT prolongation as they lead to decreased activity of factors II, VII, IX, and X. Inherited deficiencies of these clotting factors are very rare.

(Choice G) The TT measures the rate of conversion of fibrinogen to fibrin. It is prolonged in patients with deficient or defective fibrinogen, which can be congenital or acquired. The most common cause of acquired dysfibrinogenemia is liver disease.

Educational objective:

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V, VII, and X. Vitamin K deficiency and warfarin anticoagulant therapy are common causes of isolated PT prolongation as they lead to decreased activity of factors II, VII, IX, and X. Inherited deficiencies of these clotting factors are very rare.

(Choice G) The TT measures the rate of conversion of fibrinogen to fibrin. It is prolonged in patients with deficient or defective fibrinogen, which can be congenital or acquired. The most common cause of acquired dysfibrinogenemia is liver disease.

Educational objective:

Hemophilia is an X-linked recessive coagulopathy that presents with intramuscular hemorrhage, hemarthroses, and delayed bleeding after procedures. Laboratory results show partial thromboplastin time prolongation; other tests of hemostatic function are generally normal.

References

- Bleeding and bruising: a diagnostic work-up.
- Diagnosis and management of von Willebrand disease: guidelines for primary care.

Pathology	Hematology & Oncology	Hemophilias
Subject	System	Topic

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A 22-year-old woman comes to the office due to worsening dyspnea and heart pounding with exercise for the last week. She has no chronic medical conditions but reports aches and pains over the past several weeks. The patient takes ibuprofen as needed but no other medications. Temperature is 37.2 C (99 F), blood pressure is 138/86 mm Hg, and pulse is 90/min. BMI is 18 kg/m^2. Physical examination shows an erythematous rash in sun-exposed regions. The lungs are clear to auscultation. A midsystolic click and systolic murmur are heard best at the apex without radiation. There is mild tenderness of joints. Laboratory results are as follows:

Hemoglobin	7.8 g/dL
Reticulocytes	6%
Platelets	205,000/mm^3
Leukocytes	11,200/mm^3
Creatinine	1.4 mg/dL

Which of the following is the most likely cause of this patient's hematologic findings?

A. Bone marrow suppression (3%)

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Hemoglobin	7.8 g/dL
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Platelets	205,000/mm^3
Leukocytes	11,200/mm^3
Creatinine	1.4 mg/dL

Which of the following is the most likely cause of this patient's hematologic findings?

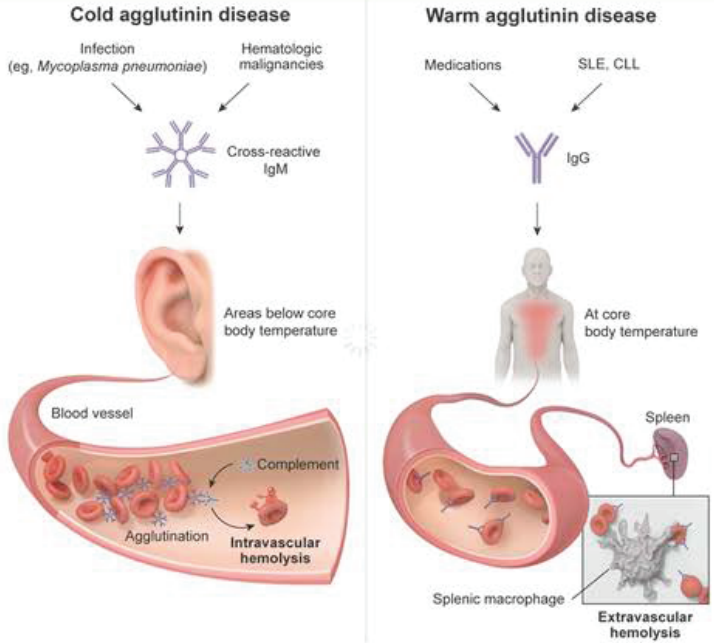
A. ~~Bone marrow suppression~~ (3%)
B. Extravascular hemolysis (45%)
C. ~~Intrinsic factor antibodies~~ (7%)
D. ~~Thrombotic microangiopathy~~ (17%)
E. Traumatic intravascular hemolysis (26%)

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Cold agglutinin disease Warm agglutinin disease

Exhibit Display



CLL = chronic lymphocytic leukemia; SLE = systemic lupus erythematosus.

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This patient with dyspnea and heart pounding with exercise has **symptomatic anemia**. Her other findings, including the presence of joint pain, a photosensitive rash, and mild renal insufficiency, raise suspicion for **systemic lupus erythematosus** (SLE), an autoimmune disease primarily seen in **young women**. SLE frequently causes anemia due to a combination of factors, including chronic inflammation (anemia of chronic disease), gastrointestinal serositis (iron deficiency from bleeding), and/or **autoimmune hemolytic anemia** (AIHA).

Approximately 10% of patients with SLE develop AIHA due to immune dysregulation, which results in the formation of **IgG autoantibodies** against the erythrocyte membrane. Erythrocytes coated with IgG are subsequently identified by the Fc-receptor on **splenic macrophages** and partially or wholly phagocytized, leading to **extravascular hemolysis**. Laboratory assessment typically reveals **elevated reticulocyte count** (ie, reticulocytosis) because interstitial fibroblasts in the kidney sense tissue hypoxia and increase the release of erythropoietin; this drives the bone marrow to increase erythrocytosis, leading to the presence of immature red cells in the peripheral blood (normoblasts, reticulocytes).

(Choices A and C) The presence of significant reticulocytosis (eg, >4-5%) rules out causes of anemia associated with an impaired bone marrow response, including bone marrow suppression from cancer or infection (eg, parvovirus), anemia of chronic disease (cytokine-mediated retention of iron), and vitamin

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associated with an impaired bone marrow response, including bone marrow suppression from cancer or infection (eg, parvovirus), anemia of chronic disease (cytokine-mediated retention of iron), and vitamin deficiency (eg, vitamin B_{12} deficiency from intrinsic factor antibodies, iron deficiency).

(Choice D) A normal platelet count effectively rules out anemia due to a microangiopathic process associated with intravascular platelet consumption (eg, thrombotic microangiopathy).

(Choice E) Although traumatic intravascular hemolysis can occur with a mechanical heart valve or severe aortic stenosis, it is uncommon in otherwise healthy young individuals. Furthermore, this patient's heart murmur is most consistent with mitral valve prolapse, which is common in patients with SLE but rarely causes traumatic hemolysis.

Educational objective:
Anemia with an elevated reticulocyte count (ie, reticulocytosis) indicates that the bone marrow is responding appropriately to the anemia by generating new erythrocytes. Reticulocytosis is commonly seen in patients with hemolysis or acute bleeding. Many other causes of anemia are associated with low reticulocyte count, including bone marrow suppression (eg, parvovirus), iron deficiency anemia, vitamin B_{12}/folate deficiency, and anemia of chronic disease.

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Pharmacology researchers develop a novel immunotherapy to treat malignancies. In this therapy, T lymphocytes are harvested from patients with a malignancy and genetically modified to express a chimeric antigen receptor composed of an extracellular antigen recognition domain linked with an intracellular T-cell signaling domain. These modified T cells are expanded *ex vivo* and then infused back into the patient, where they destroy the cancer cells. In one of the experiments, they modify the chimeric antigen receptor to recognize CD19. Use of this treatment is most likely to have which of the following potential complications?

A. Autoimmune endocrinopathy

B. Graft versus host disease

C. Hypogammaglobulinemia

D. Prolonged myelosuppression

E. Secondary malignancy

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Pharmacology researchers develop a novel immunotherapy to treat malignancies. In this therapy, T lymphocytes are harvested from patients with a malignancy and genetically modified to express a chimeric antigen receptor composed of an extracellular antigen recognition domain linked with an intracellular T-cell signaling domain. These modified T cells are expanded *ex vivo* and then infused back into the patient, where they destroy the cancer cells. In one of the experiments, they modify the chimeric antigen receptor to recognize CD19. Use of this treatment is most likely to have which of the following potential complications?

A. ~~Autoimmune endocrinopathy~~ (0%)
B. Graft versus host disease (0%)
✓ C. Hypogammaglobulinemia (100%)
D. Prolonged myelosuppression (0%)
E. Secondary malignancy (0%)

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Leukocyte surface molecules are categorized using **cluster of differentiation** (CD) nomenclature to assist with **immunophenotyping**, the differentiation of immune cells based on cell surface features (ie, with flow cytometry). Although some CD molecules are expressed on most immune cells (eg, CD45), others are restricted to a specific population of leukocytes.

CD19 is a transmembrane protein unique to **B lymphocytes** that reduces the cytokine threshold for B-cell activation and proliferation following antigen binding. Because B-cell cancers (eg, acute lymphocytic leukemia, diffuse B-cell lymphoma) often overexpress CD19 to increase replication rate, anti-CD19 immunotherapy (eg, blinatumomab) has been developed to treat these malignancies.

CAR T-cell therapy is a specific type of immunotherapy that involves the following:

1. Extraction and purification of T cells from a patient or donor
2. Genetic modification to form a **chimeric antigen receptor** (CAR), which combines an extracellular antigen recognition domain for an antigen overexpressed in a tumor with an intracellular stimulatory T-cell signaling domain that promotes T-cell activation/proliferation and tumor-killing activity.
3. Reinfusion of the modified T cells into the patient

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T-cell signaling domain that promotes T-cell activation/proliferation and tumor-killing activity.

3. Reinfusion of the modified T cells into the patient

Binding the modified T-cell to its tumor antigen stimulates the release of inflammatory cytokines and promotes destruction of the cancer cell. The most serious adverse effect is a **life-threatening cytokine storm**, which must be countered with urgent anti–IL-6 treatment (eg, tocilizumab) to prevent death. In addition, anti-CD19 therapy in particular can also cause **hypogammaglobulinemia** due to destruction of healthy B cells/plasma cells.

(Choice A) Autoimmune endocrinopathy sometimes occurs with immune checkpoint inhibitor therapy, which targets surface molecules (eg, PD-1, CTLA-4) on cytotoxic T cells. CD19 is only expressed on B-cells, not T-cells.

(Choice B) Graft versus host disease occurs when allogeneic (non-self) immune cells attack host tissue. It does not occur with autologous immune cells because these cells are drawn from the patient and adequately differentiate self from non-self.

(Choice D) Chemotherapy often causes transient myelosuppression due to destruction of rapidly dividing hematopoietic cells. Anti-CD19 therapy may reduce B-cell populations but does not significantly affect other hematologic cells.

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(Choice B) Graft versus host disease occurs when allogeneic (non-self) immune cells attack host tissue. It does not occur with autologous immune cells because these cells are drawn from the patient and adequately differentiate self from non-self.

(Choice D) Chemotherapy often causes transient myelosuppression due to destruction of rapidly dividing hematopoietic cells. Anti-CD19 therapy may reduce B-cell populations but does not significantly affect other hematologic cells.

(Choice E) Chemotherapy and radiation therapy can damage DNA of healthy cells, leading to secondary malignancy several months or years later. CD19 therapy is targeted to B cells and is unlikely to lead to secondary malignancy because it does not damage DNA.

Educational objective:
Chimeric antigen receptor (CAR) T-cell therapy involves extracting T cells from a patient with malignancy, inserting a CAR gene against a protein overexpressed by the malignancy, and then reinfusing the modified T cells back into the patient. CAR T-cell therapy against CD19 is used to treat B-cell malignancy because CD19 is expressed only by B cells.

References

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A 58-year-old man comes to the emergency department due to wound dehiscence. The patient had a left subclavian catheter port placed 3 months ago to begin bevacizumab infusions for recurrent glioblastoma. The incision wound closed completely but has now partially reopened. Vital signs are normal. Examination of the left side of the chest reveals that 50% of the incision has opened; subcutaneous tissue and part of the port are visible, but there is no drainage from the wound or erythema of the surrounding skin. A complication of bevacizumab is suspected. Which of the following is the most likely primary mechanism of this patient's wound dehiscence?

A. Depletion of endothelial growth factors for angiogenesis
B. Eccentric myointimal proliferation and luminal obstruction of the arterioles
C. Impaired cytoskeleton microtubule development
D. Impaired inflammatory cell migration to the wound site
E. Inadequate hydroxylation of collagen polypeptides

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A 58-year-old man comes to the emergency department due to wound dehiscence. The patient had a left subclavian catheter port placed 3 months ago to begin bevacizumab infusions for recurrent glioblastoma. The incision wound closed completely but has now partially reopened. Vital signs are normal. Examination of the left side of the chest reveals that 50% of the incision has opened; subcutaneous tissue and part of the port are visible, but there is no drainage from the wound or erythema of the surrounding skin. A complication of bevacizumab is suspected. Which of the following is the most likely primary mechanism of this patient's wound dehiscence?

- A. Depletion of endothelial growth factors for angiogenesis (78%)
- B. Eccentric myointimal proliferation and luminal obstruction of the arterioles (1%)
- C. Impaired cytoskeleton microtubule development (4%)
- D. Impaired inflammatory cell migration to the wound site (9%)
- E. Inadequate hydroxylation of collagen polypeptides (6%)

78% 01 min, 08 secs 03/20/2021

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Wound dehiscence is partial or complete separation of previously approximated wound edges. It occurs due to disruption of the wound-healing process and may be a complication of medications such as bevacizumab.

Bevacizumab is a monoclonal antibody that **binds vascular endothelial growth factor (VEGF)**, preventing it from binding to its cell surface receptor. This **inhibits angiogenesis**—the process by which new blood vessels sprout from surrounding, uninjured vessels and grow into the wound—because angiogenesis is largely stimulated by VEGF.

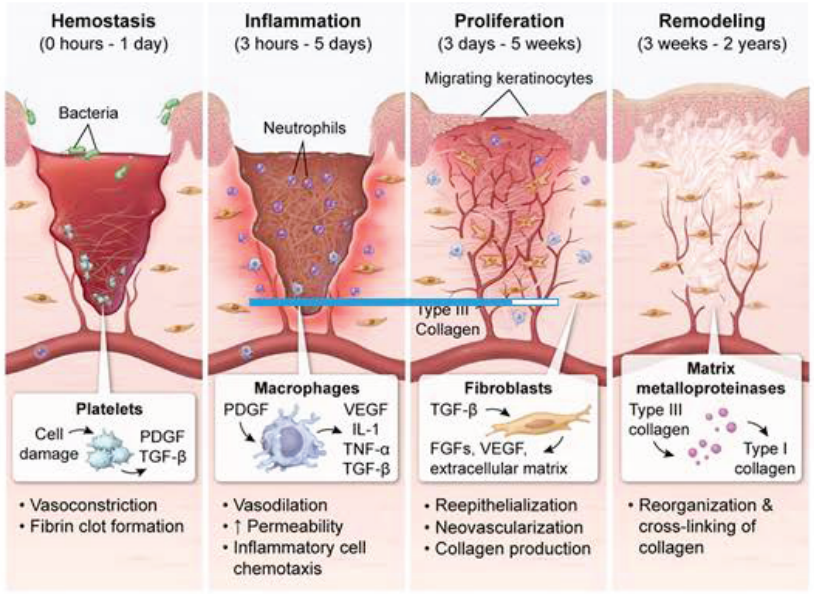
Because bevacizumab suppresses the growth of new blood vessels, it limits the blood supply to the tumor and is often referred to as cancer-starving therapy. However, because it also suppresses angiogenesis in healing wounds, it can cause wound dehiscence. The lack of angiogenesis leads to **inadequate blood supply** to support **collagen production** during the proliferation phase (3 days to 5 weeks) and collagen **remodeling and cross-linking** during the maturation phase (3 weeks to 2 yr). When these are inhibited, the **tensile strength** of the wound remains **low**, and dehiscence can occur even weeks to months after initial wound closure.

(Choice B) Radiation therapy, commonly used in cancer treatment, causes DNA damage, resulting in

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Phases of wound healing



FGF = fibroblast growth factor; **PDGF** = platelet-derived growth factor; **TGF-β** = transforming growth factor-beta; **VEGF** = vascular endothelial growth factor.

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initial wound closure.

(Choice B) Radiation therapy, commonly used in cancer treatment, causes DNA damage, resulting in apoptosis of susceptible (eg, highly proliferative) cells. However, it also damages surrounding noncancerous tissues, including local blood vessels, which can subsequently develop progressive eccentric myointimal proliferation and luminal obstruction. This can eventually result in tissue ischemia (eg, chronic skin ulcers).

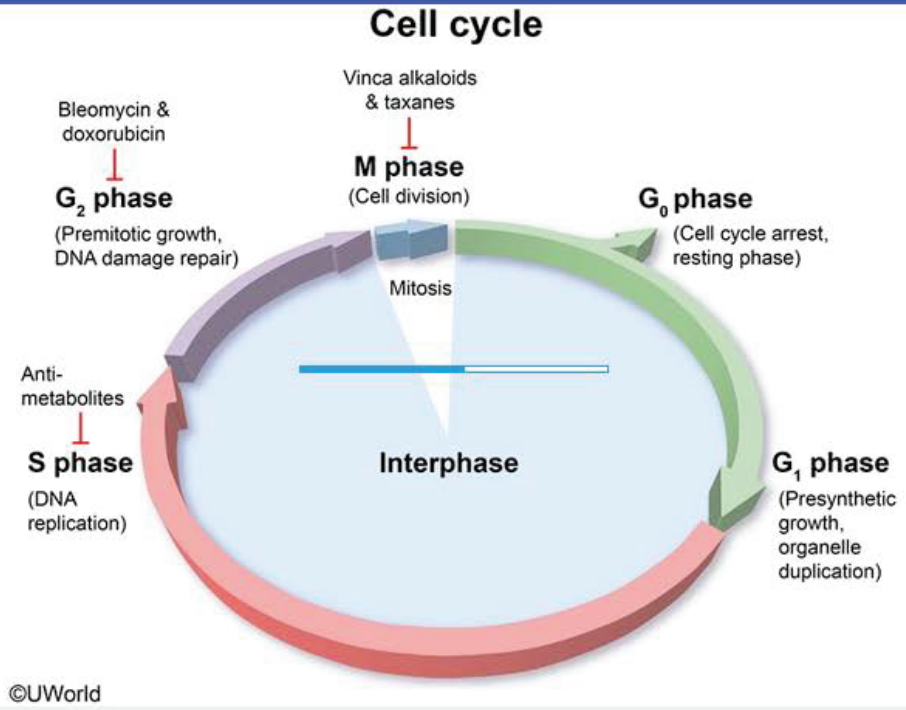
(Choice C) Vinca alkaloids such vincristine and vinblastine inhibit cytoskeleton microtubule development. This results in the arrest of cell division and replication at the metaphase stage, leading to failure of division and cell death.

(Choice D) Anti-inflammatory agents such as glucocorticoids can impair inflammatory cell migration to the wound site. Suppression of inflammation, the wound-healing phase that precedes proliferation, can delay the progression of wound healing.

(Choice E) Vitamin C deficiency can result in inadequate hydroxylation of proline and lysine residues during collagen synthesis. Because hydroxyproline and hydroxylysine are essential for collagen cross-linking, vitamin C deficiency compromises collagen cross-linking and reduces the maximal tensile strength of the wound.

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and cell death.

(Choice D) Anti-inflammatory agents such as glucocorticoids can impair inflammatory cell migration to the wound site. Suppression of inflammation, the wound-healing phase that precedes proliferation, can delay the progression of wound healing.

(Choice E) Vitamin C deficiency can result in inadequate hydroxylation of proline and lysine residues during collagen synthesis. Because hydroxyproline and hydroxylysine are essential for collagen cross-linking, vitamin C deficiency compromises collagen cross-linking and reduces the maximal tensile strength of the wound.

Educational objective:
Bevacizumab is a monoclonal antibody that inhibits the binding of vascular endothelial growth factor (VEGF) to its receptor. This inhibits angiogenesis and limits blood supply to tumors (ie, cancer-starving therapy). However, it also impairs wound healing and can lead to wound dehiscence.

Pharmacology	Hematology & Oncology	Wound healing
Subject	System	Topic

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A 48-year-old woman is evaluated for a painless left breast mass. Physical examination shows a 4-cm mass with dimpling of the overlying skin; left axillary lymphadenopathy also is noted. Breast imaging reveals a spiculated soft tissue mass with microcalcifications. Biopsy of the mass demonstrates invasive ductal carcinoma. Immunohistochemistry of the tissue sample shows the tumor cells are negative for estrogen and progesterone receptors but overexpress the *HER2* epidermal growth factor receptor. The patient is treated with systemic chemotherapy and a monoclonal antibody drug that binds the extracellular domain of the growth factor receptor. Repeat evaluation 6 weeks later shows a decrease in the size of the breast mass. Which of the following host factors are primarily responsible for mediating the response to the monoclonal antibody therapy?

A. B lymphocytes and immunoglobulins

B. $CD8^+$ T lymphocytes and interferon gamma

C. Natural killer cells and granzymes

D. Polymorphonuclear leukocytes and lysosomes

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A 46-year-old woman is evaluated for a painless left breast mass. Physical examination shows a 4-cm mass with dimpling of the overlying skin; left axillary lymphadenopathy also is noted. Breast imaging reveals a spiculated soft tissue mass with microcalcifications. Biopsy of the mass demonstrates invasive ductal carcinoma. Immunohistochemistry of the tissue sample shows the tumor cells are negative for estrogen and progesterone receptors but overexpress the *HER2* epidermal growth factor receptor. The patient is treated with systemic chemotherapy and a monoclonal antibody drug that binds the extracellular domain of the growth factor receptor. Repeat evaluation 6 weeks later shows a decrease in the size of the breast mass. Which of the following host factors are primarily responsible for mediating the response to the monoclonal antibody therapy?

A. B lymphocytes and immunoglobulins (16%)

B. $CD8^+$ T lymphocytes and interferon gamma (35%)

✓ C. Natural killer cells and granzymes (38%)

D. Polymorphonuclear leukocytes and lysosomes (9%)

Correct

38%
Answered correctly

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HER2 is an epidermal growth factor receptor overexpressed by aggressive breast cancers. Treatment with a **monoclonal antibody** (eg, trastuzumab) that targets the *HER2* surface receptor often results in tumor regression. Although antibody binding can trigger cancer cell death through a variety of mechanisms (eg, receptor downregulation, complement deposition), much of the response is due to **antibody-dependent cellular cytotoxicity** (ADCC).

ADCC classically involves the following:

1. A naturally occurring or monoclonal **IgG** binds to a complementary surface antigen on a host or foreign cell.
2. A patrolling **natural killer** (NK) cell binds the **Fc portion** of the attached IgG using **CD16**.
3. Binding triggers the NK cell to release its **granules**, which contain perforin and **granzymes** (proteases) that induce apoptosis/osmotic lysis of the antibody-bound cell.

Although NK cells are derived from the same lymphocyte lineage as B- and T-cells, they are considered part of the **innate immune system** because they do not engage with major histocompatibility complexes (MHCs) to differentiate self from nonself. Unlike cytotoxic T-cells, NK cells can often identify neoplasms that have downregulated surface expression of MHC-I molecules.

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part of the **innate immune system** because they do not engage with major histocompatibility complexes (MHCs) to differentiate self from nonself. Unlike cytotoxic T-cells, NK cells can often identify neoplasms that have downregulated surface expression of MHC-I molecules.

(Choice A) Tumor-infiltrating B cells release inflammatory cytokines, display tumor-associated antigens, and generate tumor-specific immunoglobulin. They do not mediate responses to monoclonal antibodies.

(Choice B) CD8 cells release effector cytokines (eg, interferon gamma, tumor necrosis factor) and cytotoxic granules (eg, perforin, granzymes) that destroy tumor cells. However, they interact with the MHC class I receptor, not the Fc portion of monoclonal immunoglobulin.

(Choice D) Macrophages and neutrophils also have CD16 and engage in ADCC and CD16-mediated phagocytosis of foreign organisms. However, their role in antitumor activity is unclear. The efficacy of monoclonal antibody therapy is thought to be largely mediated by NK-cell ADCC.

Educational objective:
Cancer immunotherapy often includes the administration of monoclonal antibodies against a target overexpressed on the cancer cell surface. The Fc portion of the bound antibody is identified by natural killer cells via CD16, leading to antibody-dependent cellular cytotoxicity via the release of granzymes and perforin.

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A 2-day-old boy is being examined in the newborn nursery prior to discharge from the hospital. He was born at 38 weeks gestation by vaginal delivery. The pregnancy and delivery were uncomplicated, and the boy has been breastfeeding, stooling, and urinating normally. The patient's mother has beta-thalassemia trait, and his father has a normal hemoglobin electrophoresis. Vital signs and physical examination are normal. Which of the following hemoglobin compositions is most likely predominant in this infant?

- A. $\alpha_2\beta_2$ (15%)
- ✓ B. $\alpha_2\gamma_2$ (78%)
- C. $\alpha_2\delta_2$ (4%)
- D. β_4 (0%)
- E. γ_4 (0%)
- F. $\zeta_2\varepsilon_2$ (0%)
- G. $\zeta_2\gamma_2$ (0%)

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Hemoglobin

Type	Name	Components
Embryonic	Gower 1	ζ2ε2
	Portland	ζ2γ2
	Gower 2	α2ε2
Fetal	F*	α2γ2
Adult	A	α2β2
	A2*	α2δ2
α-thalassemia intermedia	H	β4
α-thalassemia major	Barts	γ4

*Predominant in β-thalassemia.

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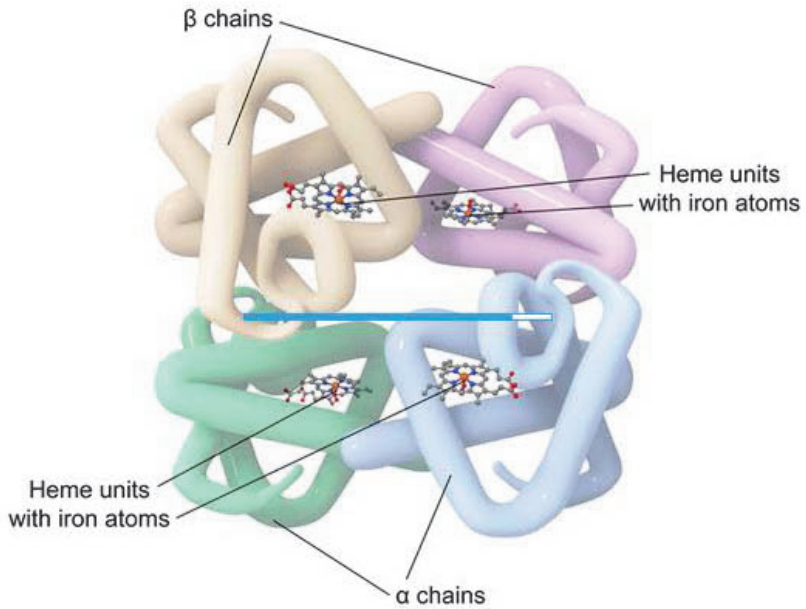
Hemoglobin is a tetramer that consists of 2 pairs of globin chains (total of 4 chains per molecule

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Hemoglobin tetramer



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Hemoglobin is a tetramer that consists of 2 pairs of globin chains (total of 4 chains per molecule). During the first few weeks of embryogenesis, hemoglobin is synthesized by the yolk sac and contains zeta or epsilon globin chains **(Choices G and F)**. Thereafter, one pair of the globin chains should always be alpha and the other should be non-alpha.

Fetal hemoglobin (Hb F) production begins around 8 weeks gestation and replaces all embryonic hemoglobin by 14 weeks gestation, when erythropoiesis in the fetal liver and spleen is established. Hb F consists of 2 alpha and 2 gamma protein subunits (**α2γ2**). Production declines at birth, and Hb F comprises ~60-80% of all hemoglobin in a term newborn. Hb F is gradually replaced by adult hemoglobin (Hb A, α2β2) **(Choice A)** during the first 6 months of life, after which Hb A composes the vast majority of adult hemoglobin.

Compared to red blood cells with Hb A, those with Hb F have a **high oxygen affinity** as Hb F binds to 2,3-bisphosphoglycerate poorly. The greater affinity of Hb F facilitates transplacental oxygen delivery from the maternal circulation to that of the fetus.

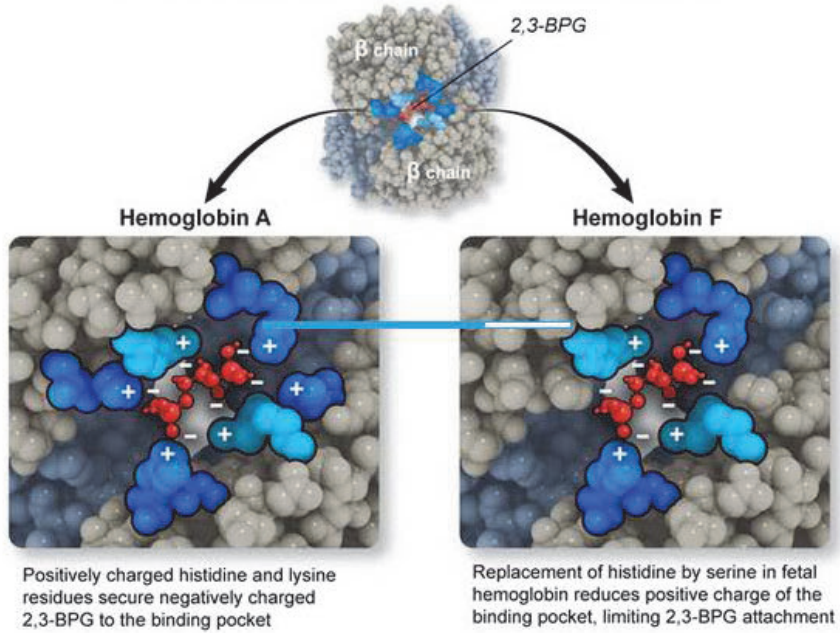
(Choice C) Hemoglobin A2 (α2δ2) is a normal hemoglobin variant that makes up 2%-3% of hemoglobin in a healthy adult and is functionally similar to Hb A. Patients with beta-thalassemia major have impaired beta globin production, resulting in an excess of alpha globin chains (eg, Hb A2, Hb F) and no Hb A.

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2,3-bisphosphoglycerate and hemoglobin binding



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(Choice C) Hemoglobin A2 (α2δ2) is a normal hemoglobin variant that makes up 2%-3% of hemoglobin in a healthy adult and is functionally similar to Hb A. Patients with beta-thalassemia major have impaired beta globin production, resulting in an excess of alpha globin chains (eg, Hb A2, Hb F) and no Hb A.

(Choices D and E) Alpha-thalassemia results from a shortage of alpha globin chains. Hemoglobin H (β4) and hemoglobin Barts (γ4) have a very high oxygen affinity and cannot release oxygen, resulting in tissue hypoxia. Hemoglobin H disease manifests as chronic hemolytic anemia. Hemoglobin Barts is incompatible with life (eg, hydrops fetalis) as normal fetal and adult hemoglobin cannot be produced.

Educational objective:

Hemoglobin F (Hb F) is the predominant hemoglobin type in the second and third trimesters of pregnancy and during the first few months after birth. Hb F consists of 2 alpha and 2 gamma protein subunits (α2γ2) and has a high affinity for oxygen, which facilitates oxygen transport across the placenta to the fetus. Hb A (α2β2) is the major hemoglobin in adults.

References

- Human embryonic, fetal, and adult hemoglobins have different subunit interface strengths. correlation with lifespan in the red cell.
- Advances in the understanding of haemoglobin switching.

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A 40-year-old woman, gravida 4 para 4, comes to the clinic due to anemia. A week ago, the patient was seen in the emergency department due to fatigue, shortness of breath, and increasingly heavy, irregular menses. Laboratory evaluation showed a hemoglobin level of 5.4 g/dL. After a transfusion with packed red blood cells, her follow-up hemoglobin level was 7.8 g/dL prior to discharge. Since then, the patient's energy and breathing have improved, and she has had no further menstrual bleeding. However, yellowing of the eyes and face has developed over the last day. Vital signs are normal. Examination reveals scleral icterus. There is no hepatosplenomegaly. Laboratory results are as follows:

Complete blood count

Hemoglobin	5.9 g/dL
Reticulocytes	7%

Liver function study

Total bilirubin	3.8 mg/dL

This patient's current symptoms are most likely due to which of the following antibody-antigen reactions?

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Reticulocytes 7%

Liver function study

Total bilirubin 3.8 mg/dL

This patient's current symptoms are most likely due to which of the following antibody-antigen reactions?

A. Blood product antibodies against the patient's ABO-group antigen (5%)

B. Blood product antibodies against the patient's minor red blood cell antigen (7%)

C. Patient's antibodies against the blood product ABO-group antigen (27%)

D. Patient's antibodies against the blood product IgA (10%)

E. Patient's antibodies against the blood product minor red blood cell antigen (49%)

Correct

49% Answered correctly

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Immunologic blood transfusion reactions

Transfusion reaction	Onset	Cause	Key features
Allergic	Minutes to hours	Preformed antibodies against blood product component	• Minor: urticaria • Major: anaphylaxis (eg, IgA-deficient recipient)
Acute hemolytic	Minutes to hours	ABO incompatibility (often clerical error)	• Fever, flank pain, hemoglobinuria • DIC • + Coombs test
Febrile nonhemolytic (most common)	Hours	Cytokine accumulation during blood storage	• Fever & chills
Transfusion-related acute lung injury	Hours	Donor antileukocyte antibodies	• Respiratory distress • Bilateral pulmonary edema

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Delayed hemolytic	Days to weeks	Anamnestic antibody response	• Often asymptomatic • Laboratory evidence of hemolytic anemia • + Coombs test

DIC = disseminated intravascular coagulation.

This patient has jaundice and hemolytic anemia a week after a transfusion, findings suggestive of a **delayed hemolytic transfusion reaction** (DHTR). This reaction occurs in patients who were **previously exposed** to a foreign, **minor red blood cell (RBC) antigen** (non-ABO) via mechanisms such as pregnancy, prior transfusion, or intravenous drug use. During the first exposure, only a low, typically undetectable, antibody response is initially mounted. On **reexposure** via transfusion, the patient's memory B cells produced a larger surge of antibodies, resulting in detectable hemolysis. This is known as an **anamnestic response**.

DHTR is usually **mild** and develops **>24 hours after transfusion**, most commonly after 1-2 weeks. Most patients are asymptomatic and diagnosed only after findings of a newly positive direct antibody (**Coombs**) test and antibody screen. Additional laboratory findings include anemia with compens reticulocytosis and evidence of hemolysis (eg, ↑ indirect bilirubin, ↑ lactate dehydrogenase).

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anamnestic response.

DHTR is usually **mild** and develops **>24 hours after transfusion**, most commonly after 1-2 weeks. Most patients are asymptomatic and diagnosed only after findings of a newly positive direct antibody **(+ Coombs**) test and antibody screen. Additional laboratory findings include anemia with compensatory reticulocytosis and evidence of hemolysis (eg, ↑ indirect bilirubin, ↑ lactate dehydrogenase).

(Choices A and B) Mild hemolysis can result from the transfusion of plasma products (eg, fresh frozen plasma, platelets), which can contain donor antibodies that target ABO or minor antigens on recipient RBCs. This reaction does not typically occur with the transfusion of packed RBCs, which this patient received, because RBCs are removed from the plasma layer and washed during the blood-separation process.

(Choice C) An acute hemolytic transfusion reaction is caused by ABO incompatibility (eg, due to clerical error). Patients naturally have preformed antibodies against foreign ABO antigens (eg, anti-B antibodies in a type A patient) that will attack antigens on mismatched donor RBCs (eg, type B donor blood). Massive hemolysis occurs within minutes to hours of transfusion, causing fever, flank pain, and hemoglobinuria.

(Choice D) Anaphylactic transfusion reactions occur within minutes of transfusion initiation and with wheezing, angioedema, and hypotension, findings not seen in this patient. This reaction ca

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received, because RBCs are removed from the plasma layer and washed during the blood-separation process.

(Choice C) An acute hemolytic transfusion reaction is caused by ABO incompatibility (eg, due to clerical error). Patients naturally have preformed antibodies against foreign ABO antigens (eg, anti-B antibodies in a type A patient) that will attack antigens on mismatched donor RBCs (eg, type B donor blood). Massive hemolysis occurs within minutes to hours of transfusion, causing fever, flank pain, and hemoglobinuria.

(Choice D) Anaphylactic transfusion reactions occur within minutes of transfusion initiation and present with wheezing, angioedema, and hypotension, findings not seen in this patient. This reaction can occur in patients with IgA deficiency due to the reaction of recipient anti-IgA antibodies against donor IgA.

Educational objective:

Delayed hemolytic transfusion reactions are usually mild, hemolytic reactions that occur >24 hours after blood transfusion. They are a type of anamnestic response (delayed immunologic response) that occurs in patients previously exposed to a minor RBC antigen (eg, previous blood transfusion, pregnancy).

References

- Transfusion reactions.

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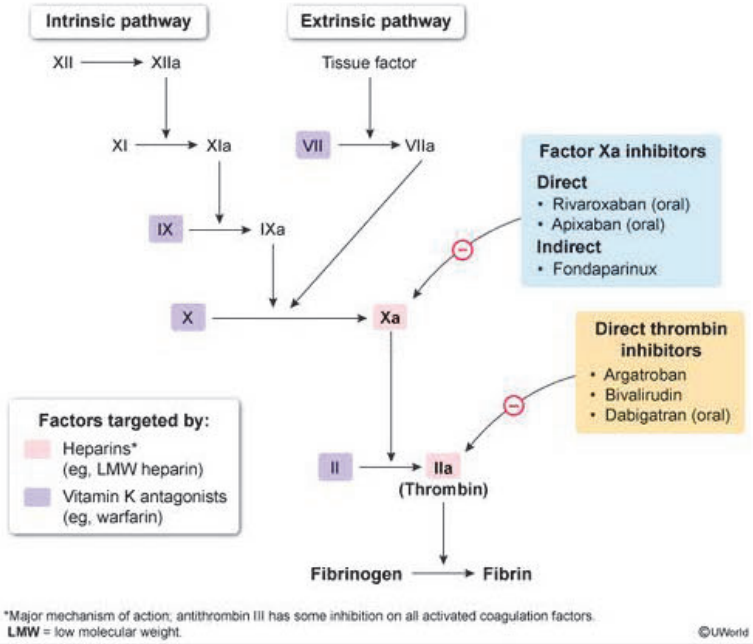
A 68-year-old man is brought to the emergency department due to sudden-onset, severe right lower extremity pain. On physical examination, the right leg is pale and cold to the touch with absent distal pulses. Cardiac auscultation reveals an irregular tachycardia, and ECG shows atrial fibrillation. Right lower extremity ultrasonography reveals an arterial embolus. Intravenous heparin infusion is initiated. This medication is most likely to cause which of the following coagulation changes?

	Thrombin time	Partial thromboplastin time (PTT)	Activity of factor Xa	
A.	~~No change~~	~~Prolonged~~	~~Decreased~~	(35%)
B.	~~No change~~	~~Prolonged~~	~~Increased~~	(3%)
C.	~~Prolonged~~	~~No change~~	~~Increased~~	(2%)
D.	Prolonged	Prolonged	No change	(6%)
E.	Prolonged	Prolonged	Decreased	(51%)

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Anticoagulants mechanisms of action



*Major mechanism of action; antithrombin III has some inhibition on all activated coagulation factors.
LMW = low molecular weight.

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Heparin is an endogenous anticoagulant that exerts its effect **indirectly** by binding to **antithrombin III** (AT), a serine protease inhibitor that irreversibly neutralizes clotting factors. Heparin binding alters the shape of AT, which converts it from a **slow to rapid inactivator** of clotting factors and increases its activity **>1,000 fold**.

Although AT neutralizes a number of clotting factors in the intrinsic pathway, its anticoagulant effect primarily stems from the inactivation of **factor Xa** and **thrombin**. Therefore, patients who receive heparin products typically have the following coagulation changes:

- **Prolonged thrombin time:** Thrombin inactivation is strongest with unfractionated heparin infusion because the length of heparin chains in this formulation are longer, which inactivates thrombin more rapidly. Although low-molecular-weight heparin formulations contain shorter chain heparin molecules, they also inactivate thrombin but to a lesser extent.
- **Decreased activity of factor Xa:** All forms of heparin (eg, unfractionated, low molecular weight, fondaparinux) have strong activity against factor Xa. Antifactor Xa activity is usually monitored to determine when adequate anticoagulation is achieved.
- **Prolonged partial thromboplastin time** (PTT): Heparin primarily inhibits the intrinsic and f common clotting pathway; therefore, PTT is prolonged.

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determine when adequate anticoagulation is achieved.

- **Prolonged partial thromboplastin time** (PTT): Heparin primarily inhibits the intrinsic and final common clotting pathway; therefore, PTT is prolonged.

Unlike heparin medications, which exert their anticoagulation effects broadly through the activation of AT, direct oral anticoagulants inhibit a single enzyme in the coagulation cascade, such as thrombin (eg, dabigatran) or factor Xa (eg, rivaroxaban).

Educational objective:

Heparin is an indirect anticoagulant that alters the shape of antithrombin (AT) III, thereby converting it from a slow to rapid inactivator of clotting factors. Because AT primarily neutralizes factor Xa and thrombin, patients on heparin have decreased factor Xa activity and prolonged thrombin time/partial thromboplastin time. In contrast, direct oral anticoagulants specifically target a single enzyme in the coagulation cascade, such as thrombin (eg, dabigatran) or factor Xa (eg, rivaroxaban).

Pharmacology	Hematology & Oncology	Anticoagulants
Subject	System	Topic

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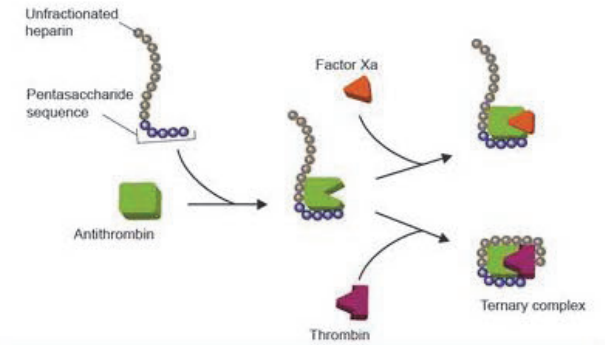
A 52-year-old man comes to the emergency department (ED) due to 2 hours of burning substernal pain. Before coming to the ED, he took several tablets of antacid at home without any relief. The patient's other medical problems include hypertension and hyperlipidemia. His temperature is 36.7 C (98 F), blood pressure is 160/90 mm Hg, and pulse is 92/min. Cardiovascular examination shows normal S1 and S2 without any murmurs. There is no abdominal tenderness. ECG shows ST-segment depression in leads II, III, and aVF. Troponin is 0.06 ng/mL (normal <0.01 ng/mL). As part of this patient's treatment, enoxaparin therapy is initiated. This drug is expected to bind to which of the following substances in this patient's blood?

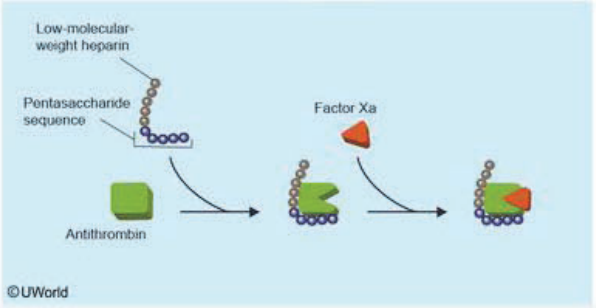
- A. Antithrombin III (73%)
- B. ~~Fibrin~~ (4%)
- C. ~~Plasminogen~~ (3%)
- D. ~~Protein C~~ (1%)
- E. Prothrombin (16%)

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Heparin's mechanism of action





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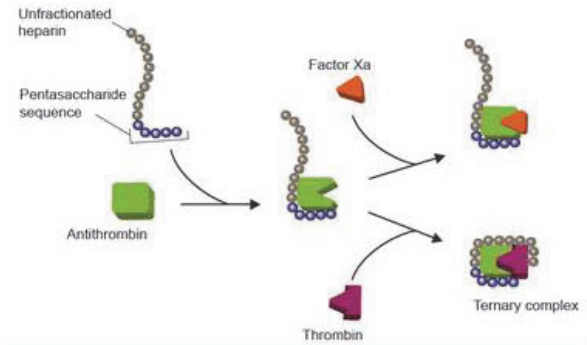
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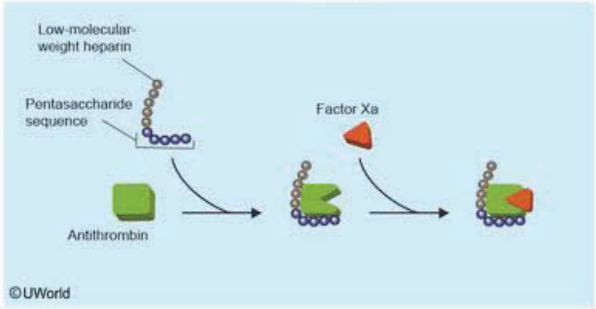
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Antithrombin

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Heparin's mechanism of action





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This patient with chest pain, ST depressions, and mild troponin elevation appears to be experiencing a myocardial infarction. **Enoxaparin** is a form of low-molecular-weight heparin (LMWH) that, like heparin, functions by binding **antithrombin III** (AT III) via a pentasaccharide sequence. Once activated, AT III binds to **factor Xa** and stops factor Xa from converting prothrombin to thrombin. Less thrombin is produced, resulting in an anticoagulant effect.

Unfractionated heparin has more molecules than LMWH, allowing it to bind factor Xa and thrombin; it is more effective than LMWH in inactivating thrombin.

(Choices B and C) Tissue plasminogen activator (t-PA) converts plasminogen to plasmin. Plasmin functions to break down fibrin, resulting in thrombolysis. Because t-PA can only bind plasminogen strongly in the presence of fibrin, its thrombolytic action is clot specific.

(Choice D) Protein C and protein S are endogenous antithrombotic molecules that are also vitamin K-dependent. Due to their shorter half-lives in the circulation, these molecules are depleted first during initiation of warfarin therapy, causing a transient procoagulant state. For this reason, patients ar treated with heparin or LMWH during initiation of warfarin therapy.

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(Choice D) Protein C and protein S are endogenous antithrombotic molecules that are also vitamin K-dependent. Due to their shorter half-lives in the circulation, these molecules are depleted first during initiation of warfarin therapy, causing a transient procoagulant state. For this reason, patients are typically treated with heparin or LMWH during initiation of warfarin therapy.

(Choice E) Prothrombin (factor II) is a vitamin K-dependent clotting factor. This factor, along with factors VII, IX, and X, is depleted by warfarin. LMWHs inhibit prothrombin production (through factor X inhibition), but they do not directly bind prothrombin.

Educational objective:

Enoxaparin is a low-molecular-weight heparin (LMWH) that functions like heparin in that it binds and activates antithrombin III (AT III). Activated AT III binds to factor Xa and stops factor Xa from converting prothrombin to thrombin. Due to its fewer number of molecules, LMWH acts primarily on factor Xa, not thrombin.

Pharmacology	Hematology & Oncology	Anticoagulants
Subject	System	Topic

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A 26-year-old woman is being treated for glomerulonephritis, photosensitive skin rash, and arthralgias. Rapid plasma reagin (RPR) test is repeatedly positive in this patient despite negative *Treponema pallidum* enzyme immunoassay (TP-EIA) testing. Coagulation study results are as follows:

Bleeding time	Normal
Activated partial thromboplastin time	Prolonged
Prothrombin time	Normal
Platelets	240,000/μL

This patient is at greatest risk for which of the following complications?

A. Esophageal dysmotility (3%)
B. Menorrhagia (8%)
C. Painful hemarthroses (18%)
D. Recurrent miscarriages (58%)

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Prothrombin time	Normal
Platelets	240,000/μL

This patient is at greatest risk for which of the following complications?

- A. Esophageal dysmotility (3%)
- B. Menorrhagia (8%)
- C. Painful hemarthroses (18%)
- ✓ D. Recurrent miscarriages (58%)
- E. Sclerodactyly (4%)
- F. ~~Tabes dorsalis~~ (6%)

Correct

58% Answered correctly

52 secs Time Spent

12/18/2020 Last Updated

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Antiphospholipid antibody syndrome	
Clinical features	**Venous or arterial thromboembolic disease** • Deep venous thrombosis • Pulmonary embolism • Ischemic stroke/transient ischemic attack **Adverse pregnancy outcomes** • Unexplained embryonic or fetal loss • Premature birth due to placental insufficiency or preeclampsia
Laboratory findings	• **Lupus anticoagulant** effect: Paradoxical **aPTT prolongation** not reversed on plasma mixing studies • Presence of specific antiphospholipid antibodies ○ **Anticardiolipin** antibody ○ **Anti-beta2-glycoprotein-I** antibody

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Glomerulonephritis, a photosensitive skin rash, and arthralgia in a young woman are suggestive systemic lupus erythematosus (SLE). This patient's prolonged activated partial thromboplastin t and false-positive rapid plasma reagin (RPR) test further suggest the presence of circulating

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○ **Anti-beta2-glycoprotein-I** antibody

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Glomerulonephritis, a photosensitive skin rash, and arthralgia in a young woman are suggestive of systemic lupus erythematosus (SLE). This patient's prolonged activated partial thromboplastin time (aPTT) and false-positive rapid plasma reagin (RPR) test further suggest the presence of circulating **antiphospholipid antibodies**. Although antiphospholipid antibodies cause **aPTT prolongation** in vitro, they act in vivo to produce a **hypercoagulable state** due to activation of phospholipid-dependent coagulation pathways. These antibodies can also cause **false-positive results** on nontreponemal serologic syphilis tests (eg, RPR and VDRL) by reacting with cardiolipin (the dominant antigen used in these tests).

Antiphospholipid antibody syndrome (APS) is a disorder characterized by the presence of antiphospholipid antibodies in the setting of venous or arterial thromboembolism and/or recurrent pregnancy loss. APS may be a primary disorder or occur secondary to other autoimmune diseases such as SLE. Although antiphospholipid antibodies are present in 10%-30% of patients with SLE, not all exhibit the clinical syndrome.

(Choices A and E) SLE is less likely than other connective tissue diseases such as scleroderm connective tissue disease to involve the esophagus. Sclerodactyly is also more typical of the CI

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Manifestations of systemic lupus erythematosus	
Clinical symptoms	• Constitutional: fever, fatigue & weight loss • Symmetric, migratory arthritis • Skin: butterfly rash & photosensitivity • Serositis: pleurisy, pericarditis & peritonitis • Thromboembolic events (due to vasculitis & antiphospholipid antibodies) • Neurologic: cognitive dysfunction & seizures
Laboratory findings	• Hemolytic anemia, thrombocytopenia & leukopenia • Hypocomplementemia (C3 & C4) • Antibodies: ○ ANA (sensitive) ○ Anti-dsDNA & anti-Sm (specific) • Renal involvement: proteinuria & elevated creatinine

ANA = antinuclear antibodies; **dsDNA** = double-stranded DNA.

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(Choices A and E)
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the clinical syndrome.

(Choices A and E) SLE is less likely than other connective tissue diseases such as scleroderma or mixed connective tissue disease to involve the esophagus. Sclerodactyly is also more typical of the CREST syndrome/scleroderma.

(Choices B and C) Painful hemarthroses and/or menorrhagia would be indicative of a hypocoagulable state. Although antiphospholipid antibodies can prolong the aPTT (and sometimes prothrombin time), patients with APS experience thromboembolic events, not increased bleeding.

(Choice F) Tabes dorsalis is a manifestation of tertiary syphilis that results in sensory ataxia. The inability to confirm syphilis screening tests with more specific treponemal tests such as *Treponema pallidum* enzyme immunoassay (TP-EIA) or fluorescent treponema antibody absorption test (FTA-ABS) argues against a diagnosis of syphilis.

Educational objective:
Glomerulonephritis, a photosensitive skin rash, and arthralgias in a young woman are suggestive of systemic lupus erythematosus (SLE). Up to 30% of patients with SLE have antiphospholipid antibodies, which can cause paradoxical aPTT prolongation and a false-positive RPR/VDRL. Patients with antiphospholipid antibodies are at risk for venous and arterial thromboembolism and unexplained, recurrent

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Educational objective:
Glomerulonephritis, a photosensitive skin rash, and arthralgias in a young woman are suggestive of systemic lupus erythematosus (SLE). Up to 30% of patients with SLE have antiphospholipid antibodies, which can cause paradoxical aPTT prolongation and a false-positive RPR/VDRL. Patients with antiphospholipid antibodies are at risk for venous and arterial thromboembolism and unexplained, recurrent pregnancy loss.

Pathology	Hematology & Oncology	Antiphospholipid syndrome
Subject	System	Topic

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An 18-year-old woman collapsed while practicing for a marathon in hot, humid weather. The patient subsequently vomited 3 times and had a tonic-clonic seizure. She has no chronic medical conditions and takes no medications. The patient does not use alcohol or illicit drugs. Temperature is 40.8 C (105.4 F), blood pressure is 90/60 mm Hg, pulse is 130/min, and respirations are 22/min. The patient is profusely sweating and is confused. Pupils are sluggishly reactive to light. Cardiopulmonary examination reveals clear lungs and normal heart sounds. Laboratory results are as follows:

Complete blood count

Hemoglobin	15.8 g/dL
Platelets	90,000/mm^3
Leukocytes	10,000/mm^3

Coagulation studies

PT	20 sec
Activated PTT	43 sec

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Coagulation studies

PT	20 sec
Activated PTT	43 sec

Which of the following sets of hematologic findings is most likely to be present in this patient?

	Fibrinolysis	Thrombin production	Plasmin generation	
A.	↓	↓	↓	(21%)
B.	↓	↓	↑	(12%)
C.	↓	↑	↑	(9%)
D.	↓	↑	↓	(11%)
E.	↑	↑	↑	(36%)
F.	↑	↑	↓	(7%)

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This patient with extreme hyperthermia and seizures has **exertional heat stroke**, a life-threatening multisystem disorder caused by inadequate body heat dissipation. Severe hyperthermia increases tissue oxygen demand and metabolic rate and shunts blood away from the central organs (eg, brain, kidneys, liver, GI tract) to the skin to dissipate heat. This can lead to tissue ischemia/necrosis and the release of procoagulant proteins (eg, tissue factor), which can trigger **disseminated intravascular coagulation** (DIC).

DIC is marked by the excessive activation of the extrinsic (tissue factor) coagulation cascade, leading to the **generation of thrombin** and cross-linked fibrin clots. **Fibrinolysis is then activated** to clear the intravascular thrombi; plasminogen is converted to **plasmin**, which cuts the cross-linked fibrin-fibers and generates fibrin-degradation products (eg, elevated D-dimer). Other anticoagulant proteins (eg, protein C, protein S) are also rapidly consumed.

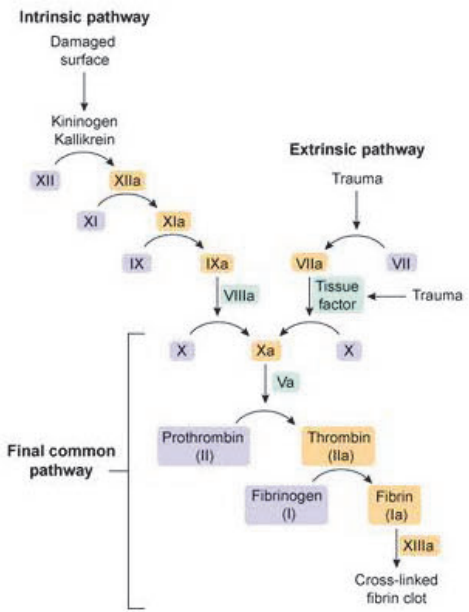
Patients with acute DIC usually have bleeding (eg, oozing from venipuncture sites) and end organ damage (eg, confusion, lung injury, renal insufficiency); laboratory studies are diagnostic and show **thrombocytopenia** (due to consumption of platelets) and **prolonged PT/PTT** (due to consumpt coagulation factors).

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Coagulation cascade pathway



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the **generation of thrombin** and cross-linked fibrin clots. **Fibrinolysis is then activated** to clear the intravascular thrombi; plasminogen is converted to **plasmin**, which cuts the cross-linked fibrin-fibers and generates fibrin-degradation products (eg, elevated D-dimer). Other anticoagulant proteins (eg, protein C, protein S) are also rapidly consumed.

Patients with acute DIC usually have bleeding (eg, oozing from venipuncture sites) and end organ damage (eg, confusion, lung injury, renal insufficiency); laboratory studies are diagnostic and show **thrombocytopenia** (due to consumption of platelets) and **prolonged PT/PTT** (due to consumption of coagulation factors).

Educational objective:
Disseminated intravascular coagulation is marked by widespread activation of the coagulation cascade, leading to excessive thrombin production and formation of microthrombi. Subsequent conversion of plasminogen to plasmin results in increased fibrinolysis to clear the thrombi. Laboratory studies show a consumption of clotting factors (prolonged PT/PTT) and platelets (thrombocytopenia) and signs of excessive fibrinolysis (eg, elevated D-dimer).

Pathophysiology	Hematology & Oncology	DIC
Subject	System	Topic

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A 50-year-old man with a long history of alcoholism is admitted to the hospital with difficulty breathing. Blood pressure is 90/40 mm Hg, pulse is 114/min, respirations are 22/min, and pulse oximetry is 92% on room air. Physical examination shows bilateral basal crackles, increased jugular venous pressure, hepatomegaly, ascites, and peripheral pitting edema. Chest x-ray demonstrates cardiomegaly. Scattered ecchymoses are present across each extremity. Laboratory results are as follows:

Platelets	120,000/mm^3
Prothrombin time	26 sec
Activated partial thromboplastin time	38 sec

The patient is given intramuscular vitamin K. Two days later, his laboratory results are unchanged. Which of the following is the most likely cause of this patient's laboratory abnormality?

- A. Dietary vitamin K deficiency (6%)
- B. Factor VII deficiency (53%)

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Platelets	120,000/mm^3
Prothrombin time	26 sec
Activated partial thromboplastin time	38 sec

The patient is given intramuscular vitamin K. Two days later, his laboratory results are unchanged. Which of the following is the most likely cause of this patient's laboratory abnormality?

- A. Dietary vitamin K deficiency (6%)
- B. Factor VII deficiency (53%)
- C. ~~Factor VIII deficiency~~ (10%)
- D. ~~Intrinsic platelet dysfunction~~ (15%)
- E. ~~Von Willebrand factor deficiency~~ (13%)

Incorrect

53%

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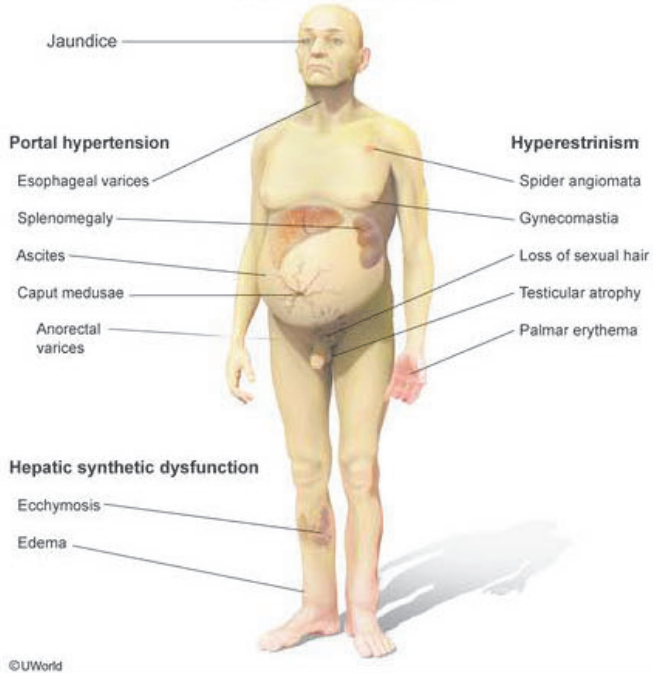
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Signs of liver cirrhosis



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This patient has **liver dysfunction** due to **alcoholism**. The liver synthesizes many proteins, including clotting factors. Chronic alcohol use leads to progressive hepatic fibrosis/**cirrhosis**, resulting in acquired coagulopathy.

Clotting factors II, VII, IX, and X are produced initially by the liver in an inactive form and then activated by vitamin K-dependent carboxylation. **Factor VII**, part of the extrinsic pathway, has the **shortest half-life** of all coagulation factors. Prothrombin time (PT) assesses the extrinsic and common pathways of coagulation and is the first to become abnormal in liver disease. This patient's PT prolongation is likely due to factor VII deficiency in the setting of cirrhosis. Because clotting factor synthesis is impaired, PT may not improve with vitamin K supplementation as there are insufficient quantities of clotting factors to undergo vitamin K-dependent carboxylation/activation.

The liver also synthesizes albumin, and hypoalbuminemia results in ascites and peripheral edema. In addition, severe cirrhosis causes high-output heart failure due to chronic splanchnic vasodilation and development of mesenteric and intrahepatic arteriovenous shunts.

(Choice A) Dietary vitamin K deficiency impairs activation of factors II, VII, IX, and X. Risk factors include severe malnourishment (eg, alcoholism) and long-term antibiotic use (alters vitamin K-producing
In vitamin K deficiency, supplementation would likely improve PT.

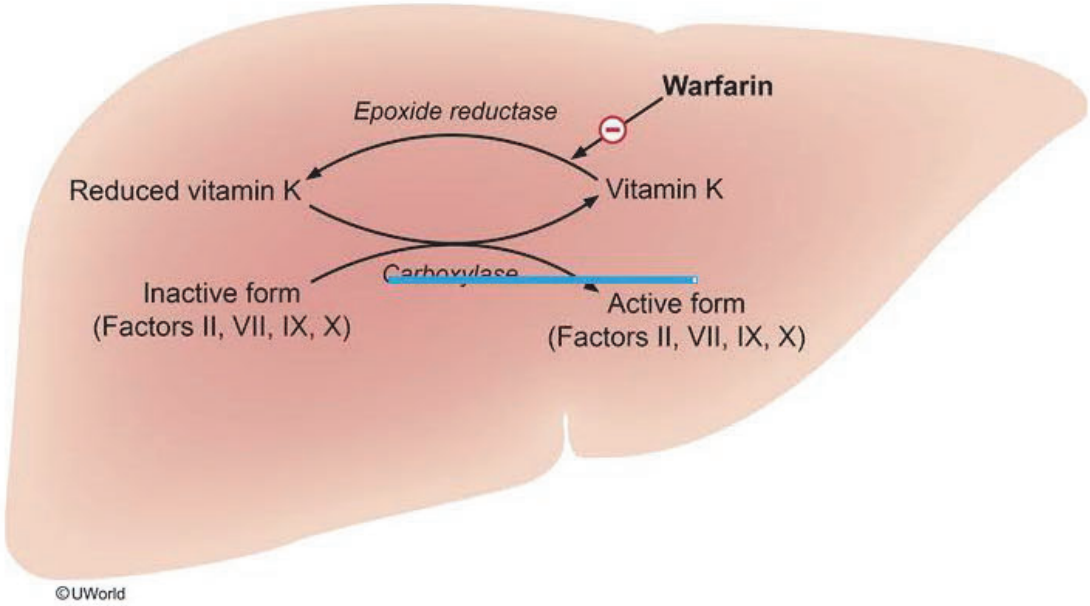
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Vitamin K



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in vitamin K deficiency, supplementation would likely improve PT.

(Choice C) In contrast to other coagulation factors, factor VIII is synthesized by endothelial cells. As part of the intrinsic pathway, factor VIII deficiency results in prolonged activated partial thromboplastin time (PTT) with a normal PT. Hemophilia A is an X-linked recessive disorder of factor VIII deficiency.

(Choice D) Cirrhosis is associated with intrinsic platelet dysfunction and thrombocytopenia due to decreased hepatic synthesis of thrombopoietin and increased splenic platelet sequestration (secondary to hypersplenism). Platelet dysfunction and significant thrombocytopenia (eg, platelets <50,000/mm^3) lead to mucocutaneous bleeding/petechiae and prolonged bleeding time but do not affect PT.

(Choice E) Von Willebrand disease causes defects in platelet adhesion and coagulation (due to associated factor VIII deficiency). PTT may be normal or prolonged based on the level of factor VIII deficiency, and platelet aggregation to ristocetin will be abnormal.

Education objective:

Vitamin K-dependent coagulation factors (II, VII, IX, and X) are synthesized in the liver. Factor VII has the shortest half-life of the coagulation factors. Failure of the prothrombin time to correct with vitamin K supplementation indicates factor VII deficiency, which is often due to underlying liver disease.

References

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A 54-year-old man comes to the emergency department with pain and swelling in the right leg. The patient has no other medical problems and takes no medications. He has smoked a pack of cigarettes daily for the past 30 years. He is a business executive and just returned from an overseas trip. Physical examination shows pitting edema of the right leg and tenderness on deep palpation of the calf muscles. Peripheral pulses are symmetric and full. He is started on a medication that prolongs activated partial thromboplastin time and prothrombin time in a dose-dependent manner but has no effect on thrombin time. Which of the following agents was this patient most likely administered?

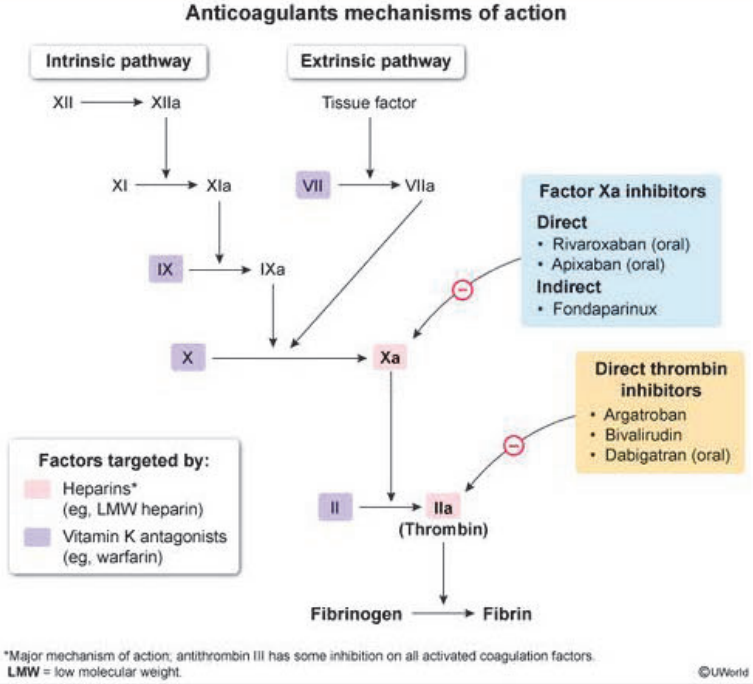
A. Cyclooxygenase inhibitor (4%)
B. Direct factor VIIa inhibitor (5%)
C. Direct factor Xa inhibitor (62%)
D. Direct thrombin inhibitor (5%)
E. Unfractionated heparin (22%)

62% 01 min, 07 secs 10/23/2020

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This patient has **deep venous thrombosis**, which is typically treated with **anticoagulation therapy for ≥3 months** to prevent recurrent thrombosis. Initial treatment is often with **heparin agents** (eg, unfractionated heparin, low-molecular-weight heparin, fondaparinux), followed by bridging to an **oral anticoagulant** (most commonly warfarin). Additional treatment options include direct factor Xa inhibitors (eg, apixaban, rivaroxaban) and direct thrombin inhibitors (eg, dabigatran).

In general, medications that affect the extrinsic pathway prolong the prothrombin time (PT), whereas inhibition of the intrinsic pathway mainly prolongs the activated partial thromboplastin time (aPTT). The thrombin time (TT) is prolonged with medications that directly or indirectly inhibit thrombin. Because factor Xa is located at the junction of the intrinsic and extrinsic pathways, **direct factor Xa inhibitors** prolong both **aPTT and PT** with no effect on TT.

(Choice A) Cyclooxygenase inhibitors (eg, aspirin) directly inhibit platelet activity and have little overall effect on aPTT, PT, or TT.

(Choice B) Direct factor VIIa inhibitors are currently in development and work by inhibiting the extrinsic pathway of the coagulation cascade. Therefore, they would prolong PT with no effect on aPTT

(Choice D) Direct thrombin inhibitors (eg, dabigatran) prevent the formation of thrombin (factor

resulting in prolongation of aPTT, PT, and TT

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effect on aPTT, PT, or TT.

(Choice B) Direct factor VIIa inhibitors are currently in development and work by inhibiting the extrinsic pathway of the coagulation cascade. Therefore, they would prolong PT with no effect on aPTT or TT.

(Choice D) Direct thrombin inhibitors (eg, dabigatran) prevent the formation of thrombin (factor IIa), resulting in prolongation of aPTT, PT, and TT.

(Choice E) Unfractionated heparin binds to antithrombin and causes inactivation of several coagulation factors, most significantly thrombin and factor Xa. As a result, aPTT and TT will be prolonged. Although the PT should theoretically be prolonged by the action of heparin on the final common pathway, in practice, the PT reagent contains heparin neutralizers that minimize this effect.

Educational objective:
Direct factor Xa inhibitors (eg, apixaban, rivaroxaban) increase the prothrombin and activated partial thromboplastin times but do not affect the thrombin time. Unfractionated heparin and direct thrombin inhibitors (eg, dabigatran) prolong the thrombin time.

References

- Developments in factor Xa inhibitors for the treatment of thromboembolic disorders

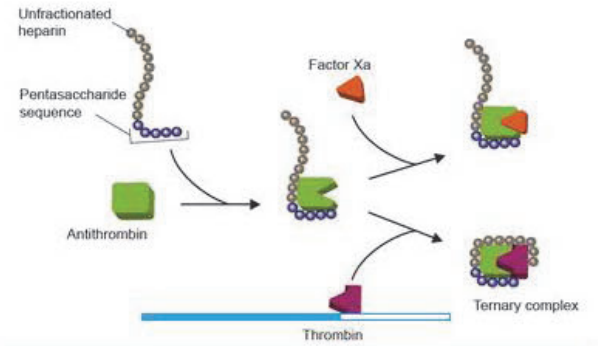
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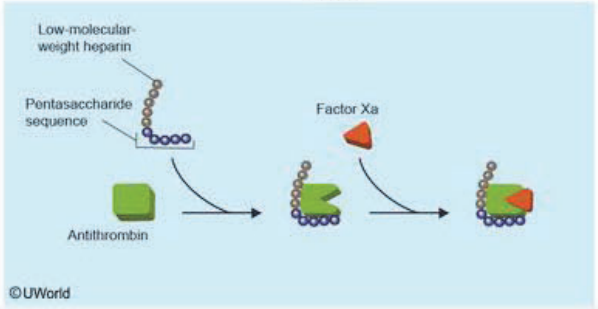
effect on aPTT, PT, or TT.

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Heparin's mechanism of action





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A 34-year-old man is brought to the emergency department after a motor vehicle collision. He has blunt abdominal trauma and bilateral femur fractures. The patient has no significant medical history and takes no medications. He does not smoke but drinks 8-12 alcoholic beverages a day. Blood pressure is 80/40 mm Hg and pulse is 110/min. Immediate resuscitation efforts are initiated, during which he receives transfusion of several units of packed red blood cells. During transport to the intensive care unit, the patient reports a tingling sensation in his fingers and toes. Serum ionized calcium level is 4 mg/dL (normal: 4.8-5.5). Which of the following is the most likely cause of this patient's current symptoms?

A. ~~Antibody-mediated red blood cell membrane damage~~ (6%)

✓ B. Calcium chelation by a substance in the transfused blood (71%)

C. Electrolyte leakage from red blood cells during pretransfusion storage (4%)

D. Increased renal tubular excretion of calcium (6%)

E. Release of intracellular contents from injured muscle (11%)

71% 01 min, 11 secs 09/28/2020

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Acute hypocalcemia	
Causes	• Neck surgery (parathyroidectomy) • Pancreatitis • Tumor lysis syndrome • Chelation: blood (citrate) transfusion
Clinical features	• Peripheral neuromuscular excitability (tetany) ○ Chvostek sign (facial muscle spasm) ○ Trousseau sign (carpopedal spasm) ○ Paresthesias, hyperreflexia • Seizures
Treatment	• IV calcium gluconate/chloride

IV = intravenous.

This patient has symptomatic hypocalcemia (eg, paresthesias) following **high-volume blood transfusion**.

Prior to storage, donated blood is generally mixed with solutions containing **citrate** anticoagulant.

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This patient has symptomatic hypocalcemia (eg, paresthesias) following **high-volume blood transfusion**. Prior to storage, donated blood is generally mixed with solutions containing **citrate** anticoagulant. Following transfusion, citrate is rapidly metabolized to bicarbonate in the liver; however, when large volumes of blood are transfused rapidly, the excess citrate can **chelate calcium** in the plasma, leading to **hypocalcemia** due to decreased serum ionized calcium concentration. This is most common with very high transfusion rates (eg, >9 units/hr), but it can also be seen at lower rates in patients with underlying hepatic insufficiency (eg, alcoholic liver disease).

Other complications of high-volume transfusion include depletion of coagulation factors and volume overload.

(Choices A and C) Antibody-mediated hemolysis is typically caused by transfusion of ABO-incompatible blood. Characteristic clinical findings include fever, back or flank pain, acute kidney injury, and hemoglobinuria. The primary electrolyte complication is hyperkalemia due to release of intracellular potassium. Hyperkalemia can also be seen due to leakage of potassium from red cells during storage. However, hypocalcemia would not occur in these scenarios.

(Choice D) Acute hypocalcemia due to increased renal calcium excretion can be seen in

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However, hypocalcemia would not occur in these scenarios.

(Choice D) Acute hypocalcemia due to increased renal calcium excretion can be seen in hypoparathyroidism. This is commonly encountered as a complication of thyroid or other neck surgery with inadvertent injury or removal of the parathyroid glands. Abdominal and lower extremity trauma would not affect parathyroid function.

(Choice E) Rhabdomyolysis typically presents with muscle pain, red urine (ie, myoglobinuria), and elevated creatine kinase. Release of intracellular phosphate from muscle cells can precipitate calcium salts in damaged muscle and lead to hypocalcemia, but this is typically a delayed finding (24-72 hours after trauma).

Educational objective:

Citrate anticoagulants in high-volume blood transfusion can chelate plasma calcium, leading to hypocalcemia which causes peripheral neuromuscular excitability (eg, paresthesia, muscle spasms). This is most common with very rapid transfusion rates, but it can also be seen at lower rates in patients with hepatic insufficiency because citrate is metabolized by the liver.

References

- Hypocalcemia in trauma patients receiving massive transfusion.

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A 26-year-old Caucasian female is found to have a single amino acid substitution (glutamine for arginine) near the protein C cleavage site in her coagulation factor V gene product. The patient is at greatest risk for developing which of the following conditions?

- A. Petechiae and ecchymoses (14%)
- B. Recurrent hemarthroses (12%)
- C. Renal artery stenosis (1%)
- D. Splenic infarction (5%)
- E. Pulmonary thromboembolism (65%)

Incorrect
Correct answer
E

65%
Answered correctly

50 secs
Time Spent

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Explanation

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The major clinical manifestations of factor V Leiden include deep vein thrombosis (DVT), cerebral vein thrombosis, and recurrent pregnancy loss. Because pulmonary thromboembolism occurs in approximately 50% of all individuals with untreated DVTs, the young woman presented here is at significant risk of developing a pulmonary thromboembolism at some point in her lifetime.

Factor V Leiden is the most common cause of inherited thrombophilia, with the heterozygote prevalence of this genetic mutation ranging from 1-9% in Caucasian populations worldwide. Heterozygote carriers of factor V Leiden have five to ten times the risk of developing a thrombosis, while homozygote carriers of factor V Leiden have fifty to one hundred times the risk of developing a thrombosis.

Factor V Leiden causes thrombophilia through two pathophysiological mechanisms. In normal hemostasis, activated protein C (APC) restricts clot formation by proteolytically inactivating factors Va and VIIIa. Factor Va Leiden has reduced susceptibility to cleavage by APC, however. Because factor Va is a cofactor in the conversion of prothrombin to thrombin, persistently circulating factor Va Leiden results in increased thrombin production. Additionally, factor V Leiden is unable to support APC anticoagulant activit

combination of increased coagulation and decreased anticoagulation produces the hypercoagul

seen in those with factor V Leiden.

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thrombin production. Additionally, factor V Leiden is unable to support APC anticoagulant activity. This combination of increased coagulation and decreased anticoagulation produces the hypercoagulable state seen in those with factor V Leiden.

(Choice A) Petechiae and ecchymoses are more consistent with qualitative or quantitative platelet abnormalities than factor V Leiden.

(Choice B) Recurrent hemarthroses are suggestive of hemophilia (factor VIII or IX deficiency), not factor V Leiden.

(Choice C) Renal artery stenosis is primarily caused by atherosclerosis and fibromuscular disease, not thrombosis. Moreover, factor V Leiden is associated with an increased risk of deep venous (not arterial) thrombosis.

(Choice D) Major causes of splenic infarction include sickle cell anemia, infectious endocarditis, and myeloproliferative disorders. Moreover, the factor V Leiden mutation is associated with deep venous (not arterial) thrombosis.

Educational Objective:

One to nine percent of Caucasians worldwide are heterozygote carriers of factor V Leiden, whicl modified to resist activated protein C. The resulting hypercoagulable state predisposes to deep

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(Choice B) Recurrent hemarthroses are suggestive of hemophilia (factor VIII or IX deficiency), not factor V Leiden.

(Choice C) Renal artery stenosis is primarily caused by atherosclerosis and fibromuscular disease, not thrombosis. Moreover, factor V Leiden is associated with an increased risk of deep venous (not arterial) thrombosis.

(Choice D) Major causes of splenic infarction include sickle cell anemia, infectious endocarditis, and myeloproliferative disorders. Moreover, the factor V Leiden mutation is associated with deep venous (not arterial) thrombosis.

Educational Objective:
One to nine percent of Caucasians worldwide are heterozygote carriers of factor V Leiden, which is modified to resist activated protein C. The resulting hypercoagulable state predisposes to deep vein thromboses, which are the source of most pulmonary emboli.

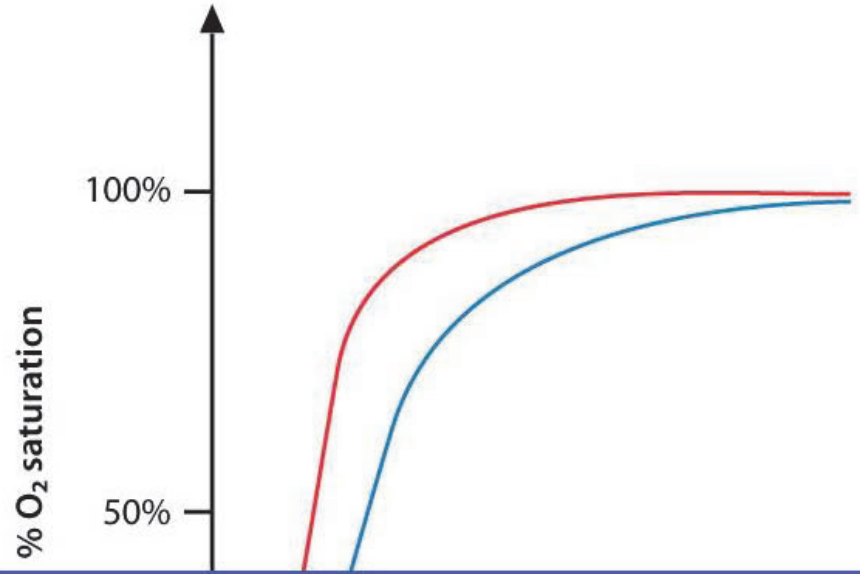
Pathology	Hematology & Oncology	Inherited thrombophilia
Subject	System	Topic

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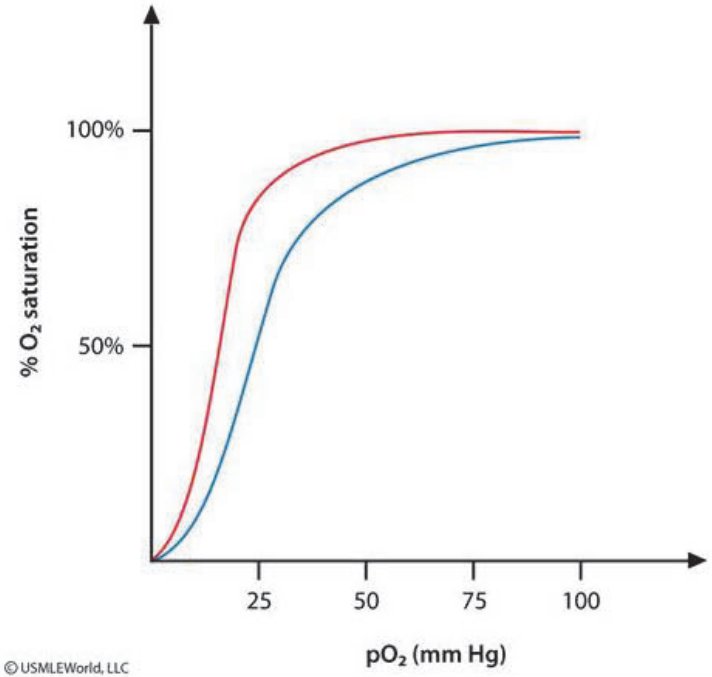
A group of investigators is researching the changes in oxygen-hemoglobin binding that occur under various clinical conditions. They are especially interested in situations that alter the shape and position of the oxygen-hemoglobin dissociation curve. Which of the following processes would most likely cause a shift from the blue curve to the red curve in the graph below?



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from the blue curve to the red curve in the graph below?

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A. Chronic high-altitude adaptation (20%)

✓ B. Hypothermia (61%)

C. Hypoventilation (5%)

D. Severe anemia (5%)

E. Strenuous exercise (7%)

Correct

61% Answered correctly

50 secs Time Spent

10/07/2020 Last Updated

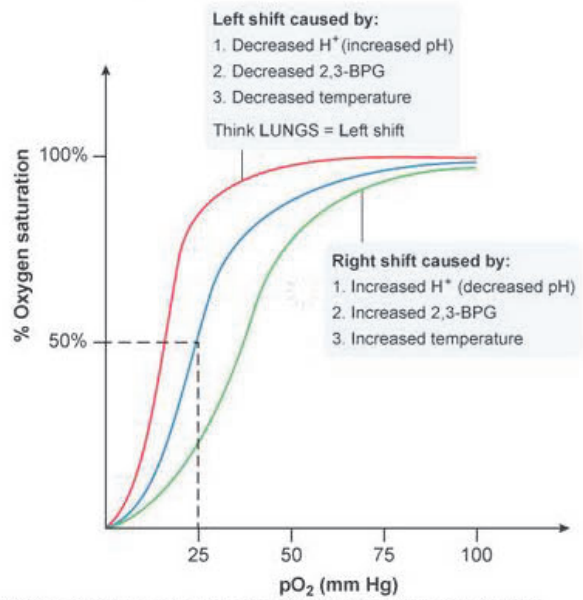
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Oxygen-hemoglobin dissociation curve



2,3-BPG = 2,3-bisphosphoglycerate; pO_2 = partial pressure of oxygen in the blood.

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pO_2 (mm Hg)

2,3-BPG = 2,3-bisphosphoglycerate; **pO_2** = partial pressure of oxygen in the blood.

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The oxygen-hemoglobin dissociation curve describes the relationship between the partial pressure of oxygen (x-axis) and the hemoglobin oxygen saturation (y-axis). Oxygen saturation increases in a sigmoidal fashion as the pO_2 increases because of the increase in oxygen-binding affinity that occurs after the first oxygen molecule binds to hemoglobin. As more oxygen molecules bind to hemoglobin, the number of available binding sites decreases and the curve eventually flattens out.

The partial pressure of oxygen in the blood at which hemoglobin is 50% saturated is known as the P_{50} (dotted black line in diagram above); this value is a standard measure of hemoglobin's affinity for oxygen and is about 26 mm Hg in normal individuals. A **leftward shift** of the oxygen-hemoglobin dissociation curve occurs when hemoglobin has **increased oxygen affinity** (ie, a lower P_{50}). Because decreased temperatures help to stabilize the bonds between oxygen and hemoglobin, **hypothermia** increases hemoglobin's oxygen affinity and shifts the dissociation curve to the left.

(Choice A) 2,3-bisphosphoglycerate (2,3-BPG) concentrations increase in erythrocytes when oxygen availability is reduced, as occurs in chronic lung disease, heart failure, and chronic exposure to l altitudes. Elevated levels of 2,3-BPG decrease hemoglobin O_2 affinity (right-shifted curve), allow

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hemoglobin's oxygen affinity and shifts the dissociation curve to the left.

(Choice A) 2,3-bisphosphoglycerate (2,3-BPG) concentrations increase in erythrocytes when oxygen availability is reduced, as occurs in chronic lung disease, heart failure, and chronic exposure to high altitudes. Elevated levels of 2,3-BPG decrease hemoglobin O_2 affinity (right-shifted curve), allowing release of additional O_2 in the peripheral tissues.

(Choices C and D) Anemia severe enough to cause lactic acidosis will result in lower blood pH, shifting the hemoglobin curve to the right. Similarly, hypoventilation causes increased CO_2 retention and respiratory acidosis that shifts the curve to the right.

(Choice E) Strenuous exercise will cause increased tissue oxidative phosphorylation, increased tissue CO_2 levels, and decreased tissue pH. This results in a shift of the dissociation curve to the right and decreased hemoglobin O_2 affinity.

Educational objective:
A left shift of the hemoglobin oxygen dissociation curve indicates increased hemoglobin O_2 affinity and can be caused by increased pH, decreased 2,3-bisphosphoglycerate, and decreased temperature. Leftward shifts of the curve inhibit the release of O_2 within peripheral tissues.

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A 54-year-old man with a history of chronic kidney disease due to hypertension develops anemia. Evaluation reveals that the cause of anemia is erythropoietin deficiency. Erythropoietin increases the numbers of erythroid precursor cells in the bone marrow and induces heme production in erythrocyte precursors. In this patient, mature erythrocytes are found that are unable to synthesize heme even though they contain detectable levels of cytoplasmic enzymes involved in heme synthesis. Lack of which of the following cellular organelles best explains this phenomenon?

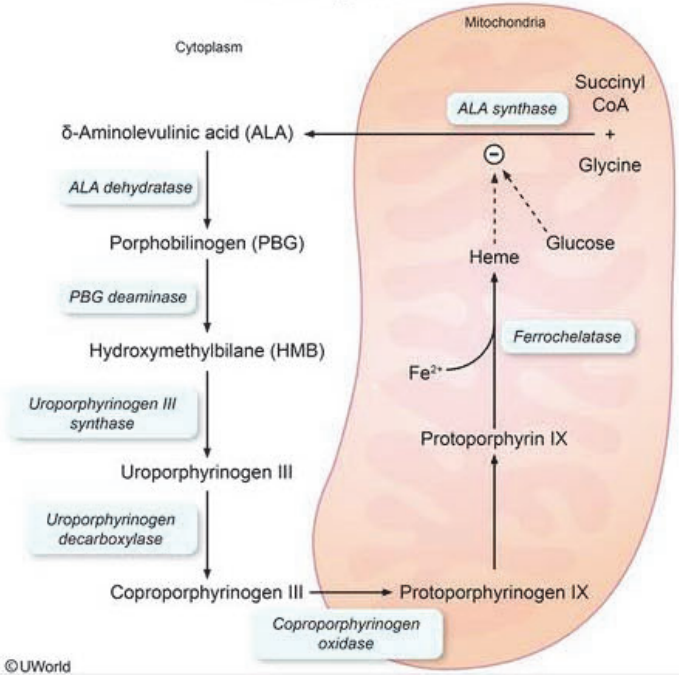
- A. Endoplasmic reticulum (14%)
- ✗ B. Golgi apparatus (5%)
- ✓ C. Mitochondria (64%)
- D. Nucleus (10%)
- E. Peroxisomes (3%)
- F. Proteasomes (1%)

Incorrect

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Heme synthesis



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Heme synthesis occurs partly in the mitochondria and partly in the cytoplasm of erythrocytes. **Mitochondria** are necessary for the first and the final 3 steps. Erythrocyte precursors divide a number of times before finally losing their nuclei and mitochondria and forming mature red blood cells that survive for about 120 days (4 months). When erythrocytes lose their mitochondria, they lose the ability to generate heme and therefore hemoglobin.

Heme is synthesized in virtually every organ, but the principal sites of synthesis are erythrocyte precursor cells (located in the bone marrow) and hepatocytes (use heme in microsomal cytochrome P450 system).

(Choices A, B, and D) Although mature erythrocytes do not contain a nucleus, a Golgi apparatus, or an endoplasmic reticulum, their cytoplasm still contains residual amounts of the enzymes necessary for heme synthesis. Therefore, the lack of mitochondria (and their associated heme biosynthetic enzymes) is a better explanation for the lack of heme synthesis.

(Choices E and F) Proteasomes are involved in protein recycling and peroxisomes are involved in fatty acid catabolism. These organelles typically disappear during erythrocyte development.

Educational objective:
Maturing erythrocytes lose their ability to synthesize heme when they lose their mitochondria, wl
necessary for the first and final 3 steps of heme synthesis.

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heme and therefore hemoglobin.

Heme is synthesized in virtually every organ, but the principal sites of synthesis are erythrocyte precursor cells (located in the bone marrow) and hepatocytes (use heme in microsomal cytochrome P450 system).

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Educational objective:
Maturing erythrocytes lose their ability to synthesize heme when they lose their mitochondria, which are necessary for the first and final 3 steps of heme synthesis.

Biochemistry	Hematology & Oncology	Heme metabolism
Subject	System	Topic

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A 15-year-old boy is found to have unexplained erythrocytosis on routine laboratory analysis. Evaluation of his immediate family shows that his father and sister also have elevated red cell levels. Genetic sequencing of the β-globin gene is performed in the affected family members. The results show a single base substitution at amino acid position 82 that replaces the normal lysine residue with methionine. Further analysis shows that this amino acid replacement impairs the ionic interaction between the β-subunit and 2,3-bisphosphoglycerate. As a result of this mutation, the patient's hemoglobin will be most similar to which of the following hemoglobin types?

A. Hemoglobin A_{1c} (2%)
B. Hemoglobin C (11%)
C. Hemoglobin F (70%)
D. Hemoglobin H (3%)
E. Hemoglobin S (12%)

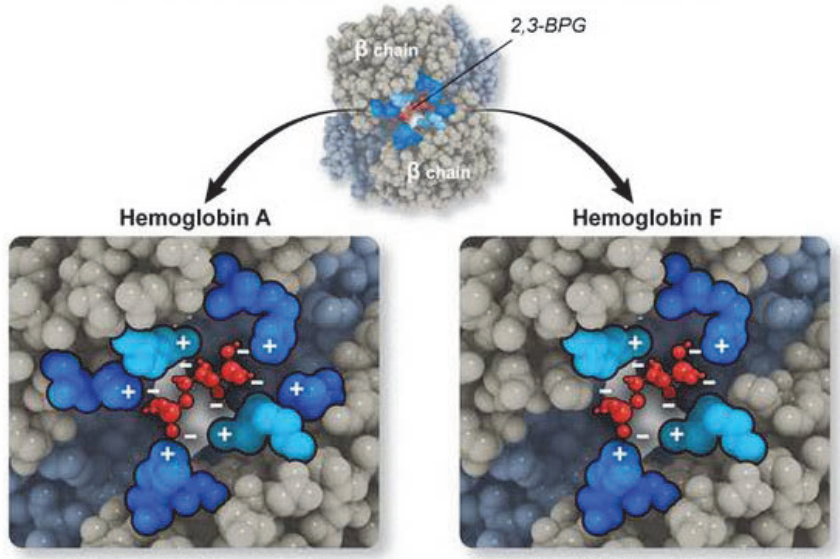
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2,3-bisphosphoglycerate and hemoglobin binding



Positively charged histidine and lysine residues secure negatively charged 2,3-BPG to the binding pocket

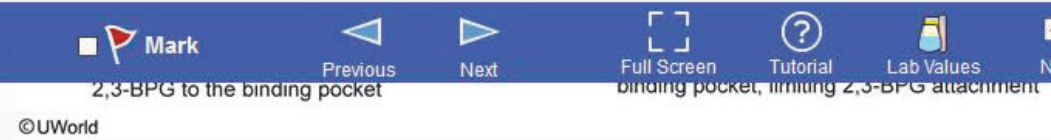
Replacement of histidine by serine in fetal hemoglobin reduces positive charge of the binding pocket, limiting 2,3-BPG attachment

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This patient most likely has **familial erythrocytosis** due to a β-globin mutation resulting in reduced binding of **2,3-bisphosphoglycerate** (2,3-BPG). 2,3-BPG is synthesized from glycolytic intermediates and binds strongly to deoxyhemoglobin in a pocket formed between the 2 beta chains. This binding reduces the oxygen affinity of hemoglobin, allowing more oxygen to diffuse into the peripheral tissues. The hemoglobin 2,3-BPG binding pocket contains positively charged amino acids (eg, histidine and lysine) that attract the negatively charged phosphate groups in 2,3-BPG. Mutations that decrease the positive charge of the binding site decrease 2,3-BPG binding and **increase hemoglobin oxygen affinity**.

Fetal hemoglobin (hemoglobin F) is synthesized primarily during fetal development (~8 weeks until term) and consists of the usual 2 alpha chains with 2 gamma chains in place of beta chains. The gamma chains do not bind effectively to 2,3-BPG due to replacement of a histidine residue with serine. As a result, fetal hemoglobin has significantly higher oxygen affinity than adult hemoglobin A. This allows fetal hemoglobin to extract more oxygen from the mother's adult hemoglobin in the placenta, providing the developing fetus with an adequate supply of oxygen.

(Choice A) Hemoglobin A_{1c} is formed by non-enzymatic glycosylation of hemoglobin A. Glycos interfere with the binding of 2,3-BPG to hemoglobin by altering the physical structure of the bind

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(Choice A) Hemoglobin A_{1c} is formed by non-enzymatic glycosylation of hemoglobin A. Glycosylation can interfere with the binding of 2,3-BPG to hemoglobin by altering the physical structure of the binding pocket, which is compensated for by increased red cell 2,3-BPG levels in patients with diabetes. However, the reduced 2,3-BPG binding affinity of this patient's mutated hemoglobin more closely resembles that of hemoglobin F.

(Choice B) Hemoglobin C results from a mutation in the β-globin chain that causes glutamate to be replaced by lysine. Hemoglobin C forms hexagonal crystals and promotes red cell dehydration, causing a mild chronic hemolytic anemia. 2,3-BPG binding and tissue oxygen delivery are not significantly altered.

(Choice D) A defect in the synthesis of alpha chains results in varying degrees of alpha thalassemia, which is characterized by the formation of β-globin and γ-globin tetramers (hemoglobin H and Barts, respectively). These abnormal tetramers have extremely high oxygen affinity (resembling myoglobin) and are ineffective at delivering oxygen to tissues.

(Choice E) Hemoglobin S is the predominant form of hemoglobin in sickle cell disease and is caused by replacement of a glutamate by valine in the β-globin chain. This results in formation of hemoglo polymers with reduced oxygen affinity.

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(Choice D) A defect in the synthesis of alpha chains results in varying degrees of alpha thalassemia, which is characterized by the formation of β-globin and γ-globin tetramers (hemoglobin H and Barts, respectively). These abnormal tetramers have extremely high oxygen affinity (resembling myoglobin) and are ineffective at delivering oxygen to tissues.

(Choice E) Hemoglobin S is the predominant form of hemoglobin in sickle cell disease and is caused by replacement of a glutamate by valine in the β-globin chain. This results in formation of hemoglobin polymers with reduced oxygen affinity.

Educational objective:

2,3-bisphosphoglycerate (2,3-BPG) normally forms ionic bonds with the beta subunits of deoxygenated hemoglobin A, facilitating oxygen release in the peripheral tissues. Mutations that result in loss of the 2,3-BPG binding pocket's positive charge cause hemoglobin A to resemble fetal hemoglobin, which binds oxygen with a higher affinity due to its inability to interact with 2,3-BPG.

Biochemistry	Hematology & Oncology	Hemoglobin properties
Subject	System	Topic

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A 45-year-old-woman comes to the office for follow-up 2 weeks after hospitalization for acute pyelonephritis. The patient was treated with morphine for pain and a course of broad-spectrum antibiotics, which she has completed. Her symptoms have now resolved. The patient also has a history of mechanical mitral valve replacement and takes warfarin. Physical examination shows no new findings. Her INR was 2.5 at the time of hospital discharge but is 6.2 today despite no change to warfarin dosage. Which of the following best explains the laboratory findings in this patient?

A. Decreased production of thromboxane A2 (1%)
B. Disruption of intestinal bacterial flora (63%)
C. Formation of anticlotting factor antibodies (3%)
D. Increased cytochrome P-450 activity (28%)
E. Increased dietary vitamin K absorption (3%)

Correct

63% Answered correctly

44 secs Time Spent

10/12/2020 Last Updated

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Warfarin is a vitamin K antagonist that inhibits epoxide reductase in the liver, thereby preventing gamma carboxylation of vitamin K–dependent clotting factors (II, VII, IX, X). This creates an anticoagulant state that is reflected on laboratory assessment as a prolonged INR. Because the effect of warfarin is significantly altered by certain foods and medications, patients on long-term warfarin are at risk for subtherapeutic or **supratherapeutic INR** due to any of the following:

- Change in dietary vitamin K intake: Increase in dietary vitamin K increases the availability of vitamin K in the liver, which counters the inhibitory effect of warfarin on epoxide reductase. Therefore, patients on warfarin are advised to eat a consistent amount of vitamin K–containing foods (eg, leafy greens, brussels sprouts).
- **Disruption to intestinal flora:** Intestinal flora produce vitamin K as a byproduct of metabolism. Therefore, antibiotics that target gram-negative bacteria such as metronidazole, macrolides, and fluroquinolones can cause supratherapeutic INR due to destruction of vitamin K–producing bacteria in the gut. In this patient, the **administration of an antibiotic** (eg, ciprofloxacin) for pyelonephritis likely destroyed gram-negative bacteria in her gut, thereby **reducing vitamin K production** and causing a supratherapeutic INR.
- Alteration to cytochrome P450 2C9 activity: Several medications induce or inhibit cytochrome P450

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the gut. In this patient, the **administration of an antibiotic** (eg, ciprofloxacin) for pyelonephritis likely destroyed gram-negative bacteria in her gut, thereby **reducing vitamin K production** and causing a supratherapeutic INR.

- Alteration to cytochrome P450 2C9 activity: Several medications induce or inhibit cytochrome P450 2C9, which alters the speed of warfarin metabolism. For instance, phenytoin, carbamazepine, and rifampin increased cytochrome P450 2C9 activity, which can result in a subtherapeutic INR **(Choice D)**. In contrast, metronidazole, fluconazole, and amiodarone inhibit cytochrome P450 2C9 activity, which can result in a supratherapeutic INR.

(Choice A) Aspirin exerts an anticoagulation effect by inhibiting the release of thromboxane A2 by platelets, which subsequently reduces platelet aggregation. This can lead to prolonged bleeding time but does not increase INR.

(Choice C) Anticlotting factor antibodies can occasionally occur due to recent pregnancy, malignancy, or rheumatologic disease. Most cases involve inhibition of factor VIII, which leads to a bleeding diathesis and prolonged aPTT (not INR, which reflects PT). This patient with a recent infection treated with antibiotics is more likely to have supratherapeutic INR due to disruption of vitamin K production by intestinal flora.

(Choice E) Increased dietary vitamin K leads to a subtherapeutic INR due to increased vitamin K

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platelets, which subsequently reduces platelet aggregation. This can lead to prolonged bleeding time but does not increase INR.

(Choice C) Anticlotting factor antibodies can occasionally occur due to recent pregnancy, malignancy, or rheumatologic disease. Most cases involve inhibition of factor VIII, which leads to a bleeding diathesis and prolonged aPTT (not INR, which reflects PT). This patient with a recent infection treated with antibiotics is more likely to have supratherapeutic INR due to disruption of vitamin K production by intestinal flora.

(Choice E) Increased dietary vitamin K leads to a subtherapeutic INR due to increased vitamin K availability in the liver.

Educational objective:
Patients on warfarin who take antibiotics that target gram-negative microorganisms (eg, metronidazole, macrolides, fluroquinolones) can develop supratherapeutic INR due to disruption of vitamin K–producing intestinal flora.

Pharmacology	Hematology & Oncology	Anticoagulants
Subject	System	Topic

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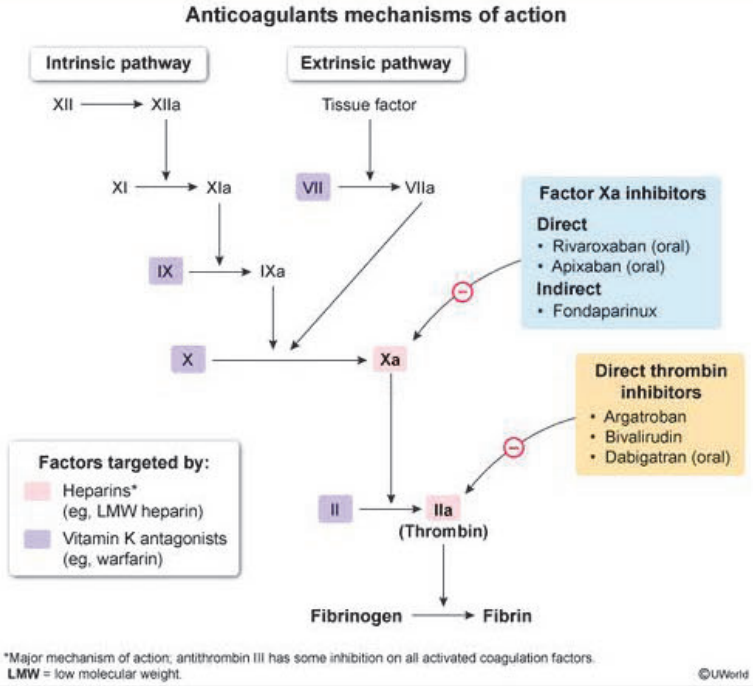
A 70-year-old man comes to the office due to palpitations. He has felt an irregular and fast heartbeat on multiple occasions over the last month. The patient has not had chest pain, dyspnea, dizziness, or weakness. His medical history includes hypertension and type 2 diabetes mellitus. Temperature is 36.7 C (98.1 F), pulse is 102/min and irregular, blood pressure is 140/82 mm Hg, and respirations are 16/min. Cardiopulmonary auscultation reveals clear lungs and no heart murmurs. ECG shows an irregularly irregular rhythm with absent P waves. The patient is started on metoprolol and apixaban. Which of the following is likely to be directly affected as the result of this therapy?

A. Conversion of factor X to Xa (58%)
B. Conversion of fibrinogen to fibrin (4%)
C. Conversion of plasminogen to plasmin (1%)
✓ D. Conversion of prothrombin to thrombin (33%)
E. Gamma-carboxylation of coagulation factors (0%)

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This patient has palpitations, an irregular pulse, and ECG findings consistent with **atrial fibrillation**. Treatment with a rate control medication (eg, metoprolol) reduces atrioventricular conduction and limits ventricular tachycardia, which helps prevent symptoms (eg, palpitations, dizziness) and risk of cardiomyopathy. However, rate control agents do not inhibit uncoordinated atrial contraction, so patients remain at risk for atrial thrombus and embolic stroke. As a result, most patients are also initiated on **anticoagulation**.

Direct factor Xa inhibitors (eg, apixaban) are often used for stroke prevention in atrial fibrillation as they are administered orally and do not require monitoring of drug levels (unlike warfarin). This class of medications blocks the active site of factor Xa, which prevents it from converting **prothrombin to thrombin**. Direct factor Xa inhibitors are denoted by names that end in "**Xa**-ban."

(Choice A) The conversion of factor X to factor Xa is the beginning the final common pathway of the coagulation cascade and is triggered by factor VIIIa (intrinsic pathway) and tissue factor (extrinsic pathway). Factor Xa inhibitors block conversion of prothrombin to thrombin, not factor X to factor Xa.

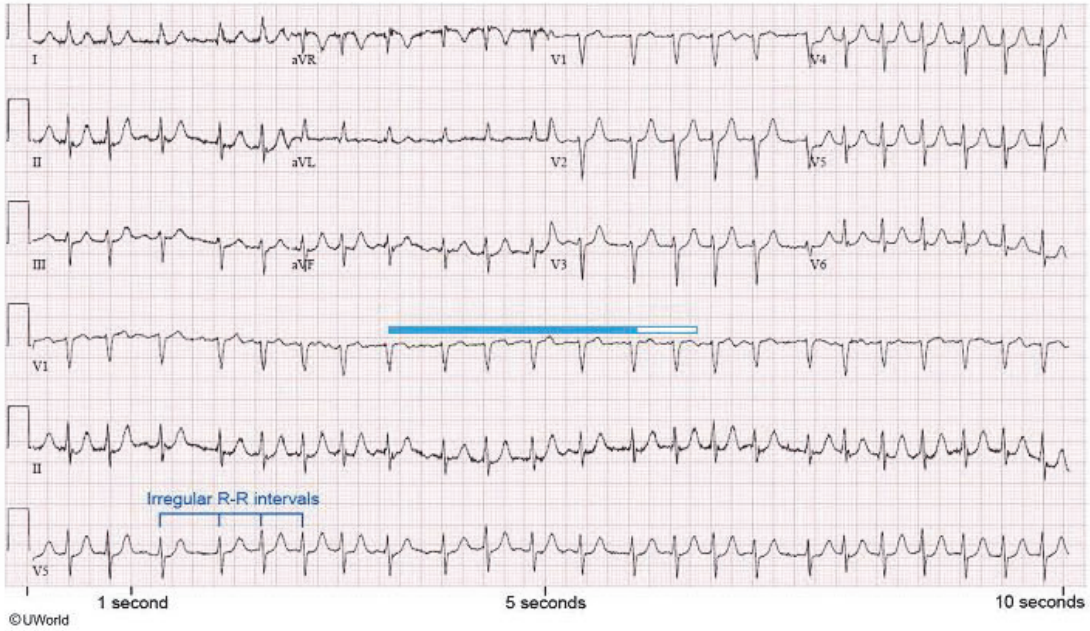
(Choice B) Factor Xa inhibitors reduce the conversion of fibrinogen to fibrin. However, this is a downstream (not direct) effect that occurs as a result of decreased thrombin levels.

(Choice C) Tissue plasminogen activator is a fibrinolytic enzyme that increases the conversion of

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(Choice C) Tissue plasminogen activator is a fibrinolytic enzyme that increases the conversion of

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(Choice B) Factor Xa inhibitors reduce the conversion of fibrinogen to fibrin. However, this is a downstream (not direct) effect that occurs as a result of decreased thrombin levels.

(Choice C) Tissue plasminogen activator is a fibrinolytic enzyme that increases the conversion of plasminogen to plasmin. It is primarily used to lyse ongoing clots in patients with acute ischemic strokes.

(Choice E) Warfarin inhibits vitamin K epoxide reductase, which decreases the reduced form of vitamin K and limits gamma-carboxylation of vitamin K–dependent coagulation factors (II, VII, IX, X).

Educational objective:
Direct factor Xa inhibitors (eg, apixaban) are anticoagulants that block the active site of factor Xa, which leads to reduced conversion of prothrombin to thrombin. This class of medications is administered orally and requires no drug level monitoring.

Physiology	Hematology & Oncology	Atrial fibrillation
Subject	System	Topic

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A 78-year-old man is found unresponsive and is brought by ambulance to the emergency department. Upon arrival, the family says he has a complicated medical history and takes multiple medications but has no known drug allergies. Noncontrast CT scan of the head reveals intracranial hemorrhage. The patient is given a recombinant biologic agent that has antigen homology with factor Xa but no catalytic effect. The agent is most likely to antagonize the effects of which of the following drugs?

- A. Apixaban (83%)
- B. ~~Aspirin~~ (0%)
- C. Dabigatran (10%)
- D. ~~Ticagrelor~~ (1%)
- E. ~~Warfarin~~ (3%)

Correct

83%
Answered correctly

01 min, 35 secs
Time Spent

10/12/2020
Last Updated

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Anticoagulation reversal for life-threatening bleeding

Drug	Mechanism of action	Reversal
Warfarin	• ↓ Production of vitamin K–dependent clotting factors	• PCC • Intravenous vitamin K
Dabigatran	• Direct inhibition of clot-bound and free thrombin	• Idarucizumab (mAb fragment that binds dabigatran) • PCC
Factor Xa inhibitors (eg, rivaroxaban, apixaban)	• Direct inhibition of factor Xa	• Recombinant modified factor Xa (eg, andexanet) • PCC
Heparin	• ↑ Activity of	• Protamine sulfate

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apixaban)		• PCC
Heparin	• ↑ Activity of antithrombin III	• Protamine sulfate

mAb = monoclonal antibody; **PCC** = prothrombin complex concentrate (contains vitamin K–dependent clotting factors).

This patient's intracranial hemorrhage was likely treated with **andexanet alfa**, a biologic agent that shares homology with factor Xa but has no proteolytic effect. It is administered to patients who have **life-threatening bleeding** while on a factor Xa inhibitor (eg, rivaroxaban, **apixaban**). The similarity of andexanet to factor Xa allows it to function as a **decoy** that binds to factor Xa inhibitors. This restores intravascular coagulation by increasing the availability of endogenous factor Xa, which converts prothrombin to thrombin and generates fibrin clots. Andexanet is reserved for life-threatening bleeding because it is associated with a significant risk of thrombosis.

(Choice B) Aspirin inhibits cyclooxygenase, which prevents platelet aggregation by blocking the generation of thromboxane A2. There is no reversal agent for aspirin widely available. Aspirin does not target factor Xa.

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(Choice B) Aspirin inhibits cyclooxygenase, which prevents platelet aggregation by blocking the generation of thromboxane A2. There is no reversal agent for aspirin widely available. Aspirin does not target factor Xa.

(Choice C) Dabigatran is a direct oral anticoagulant (DOAC) that inhibits circulating and clot-bound thrombin. It is reversed by idarucizumab, a monoclonal antibody fragment that binds to and inhibits dabigatran. Although dabigatran is a DOAC, it targets thrombin rather than factor Xa.

(Choice D) Ticagrelor blocks the $P2Y_{12}$ adenosine diphosphate receptor on the surface of platelets, which prevents platelet aggregation. Its activity is not mediated by factor Xa.

(Choice E) Warfarin is a vitamin-K antagonist that prevents the generation of vitamin–K dependent clotting factors by blocking epoxide reductase in the liver. It is reversed by the administration of vitamin K.

Educational objective:
Andexanet alfa is a factor Xa decoy that has no proteolytic effect. It is administered to patients on factor Xa inhibitors (eg, rivaroxaban, apixaban) who have life-threatening bleeding in order to reverse the anticoagulation effect.

Pharmacology	Hematology & Oncology	Anticoagulants
Subject	System	Topic

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A 15-year-old boy is brought to the emergency department with fever, purulent nasal discharge, and epistaxis. The patient has had fever and persistent nasal discharge for the past 10 days. He developed intermittent epistaxis 2 days ago that has been difficult to control. The patient has also had easy bruising for the past 2 months. Medical history is significant for cystic fibrosis, and he has not been taking his prescribed medications. Results of coagulation studies are as follows:

Prothrombin time	25 sec
Partial thromboplastin time	35 sec

Which of the following coagulation factors is most likely to be abnormal in this patient?

A. Factor V (4%)
B. Factor VII (81%)
C. Factor VIII (9%)
D. Factor XII (1%)
E. Fibrinogen (3%)

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aPTT = activated partial thromboplastin time; PT = prothrombin time.

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This patient with **cystic fibrosis** (CF) has bruising, epistaxis, and a prolonged PT, findings consistent with vitamin K deficiency. Patients with CF are at increased risk due to a predisposition to **pancreatic insufficiency**, in which viscous exocrine secretions block pancreatic ducts. Reduced secretion of pancreatic enzymes leads to **fat malabsorption** and deficiency of fat-soluble vitamins (ie, A, D, E, K).

Vitamin K normally acts as an important cofactor in the hepatic activation of coagulation **factors II, VII, IX, and X**, as well as proteins C and S. **Vitamin K deficiency** results in low levels of activated vitamin K–dependent coagulation factors, and **prolonged PT** is caused by deficiency of activated factor VII. Activated PTT (aPTT) is typically normal, as seen in this patient, although it can be prolonged with severe vitamin K deficiency (due to the effect on factor II).

Vitamin K deficiency presents with **easy bruising** and mucosal bleeding (eg, **epistaxis**). Treatment is vitamin K administration, and patients with CF also should receive pancreatic enzyme replacement therapy to improve fat-soluble vitamin absorption.

(Choice A) Factor V is not dependent on vitamin K for activation. Factor V deficiency is rare and leads to prolonged PT and aPTT.

(Choice C) Hemophilia A is an X-linked recessive disorder caused by factor VIII deficiency. As part of the

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(Choice C) Hemophilia A is an X-linked recessive disorder caused by factor VIII deficiency. As part of the intrinsic pathway, factor VIII deficiency results in prolongation of aPTT with normal PT.

(Choice D) Factor XII (ie, Hageman factor) is part of the intrinsic coagulation pathway and is not vitamin K dependent. Patients with inherited factor XII deficiency are typically asymptomatic but have prolonged aPTT.

(Choice E) Fibrinogen normally assists in coagulation via the final common pathway through fibrin clot formation and platelet binding. Fibrinogen is not dependent on vitamin K for activation. Coagulation disorders involving fibrinogen include severe liver disease and disseminated intravascular coagulation, which are associated with prolonged PT and aPTT.

Educational objective:
Patients with cystic fibrosis are at risk for fat-soluble vitamin (ie, A, D, E, K) deficiency due to fat malabsorption from pancreatic insufficiency. Vitamin K is an important cofactor in the activation of coagulation factors II, VII, IX, and X. Vitamin K deficiency leads to easy bruising, mucosal bleeding, and prolonged PT.

Pathophysiology	Hematology & Oncology	Vitamin k deficiency
Subject	System	Topic

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Physiologists conduct a study to evaluate erythropoiesis in various age groups. In one of the studies, healthy individuals who experience acute traumatic blood loss are enrolled. They divide the patients in 2 groups: younger individuals with a mean age of 35 years and older adults with a mean age of 70. These patients have normal iron, folic acid, vitamin B_{12}, and plasma protein studies. Results indicate that older patients with acute traumatic blood loss have a much lower reticulocyte count and a much longer time to recovery to pretrauma hemoglobin level when compared to younger patients. Which of the following age-related processes best explains the observed findings?

A. Decreased bone marrow mass (59%)
B. ~~Decreased medullary cavity size~~ (6%)
C. ~~Decreased red blood cell life span~~ (1%)
D. ~~Increased extramedullary hematopoiesis~~ (1%)
E. Increased marrow fibrous tissue (31%)

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Although patients with advanced age typically have normal serum blood counts, age-related changes in cytokine signaling and the cellular composition of the bone marrow **impairs the generation of new cells** in response to acute stressors such as **blood loss** or hypoxia. When compared to younger patients, the bone marrow of older patients has a **higher quantity of fat** and a **reduced overall mass**, which limits the functional reserve of hematopoietic cells. In addition, hematopoietic progenitor cell diversity and the response to stimulatory cytokines (eg, stem-cell factor, granulocyte macrophage colony-stimulating factor) are also impaired, thereby limiting the generation of new cells in response to stress. Because of these changes, older individuals cannot rapidly generate new blood cells.

(Choice B) Patients with advanced age generally have increased (not decreased) medullary cavity size due to loss of endosteal cortical bone. This increases the risk of fractures.

(Choice C) Red blood cell life span is preserved in patients with advanced age; therefore, healthy older individuals usually have normal hemoglobin level. However, they are much less capable of generating new erythrocytes in times of blood loss or other stressors (eg, hemolysis).

(Choice D) Extramedullary hematopoiesis is common in newborns but does not generally occur in older patients unless there is insufficient marrow space for hematopoietic cell proliferation. Therefore,

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individuals usually have normal hemoglobin level. However, they are much less capable of generating new erythrocytes in times of blood loss or other stressors (eg, hemolysis).

(Choice D) Extramedullary hematopoiesis is common in newborns but does not generally occur in older patients unless there is insufficient marrow space for hematopoietic cell proliferation. Therefore, extramedullary hematopoiesis is typically associated with significant bone marrow pathology (eg, myelofibrosis).

(Choice E) Although bone marrow fat increases with age, bone marrow fibrosis is not a part of normal aging. Bone marrow fibrosis is associated with primary myelofibrosis, a chronic myeloproliferative disorder marked by anemia and extramedullary hematopoiesis (hepatosplenomegaly).

Educational objective:
Patients of advanced age have increased bone marrow fat and reduced bone marrow mass, leading to impaired bone marrow reserve. This results in an inability to rapidly generate new blood cells in response to acute stress (eg, blood loss, hypoxia).

Pathophysiology	Hematology & Oncology	Aging
Subject	System	Topic

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A 57-year-old female presents to the emergency department after vomiting a substance that resembled "coffee grounds." She reports that she now feels lightheaded as well. Her past medical history is significant for deep venous thromboses, for which she takes warfarin, and occasional joint pain, for which she takes aspirin. Her blood pressure is 90/60 mm Hg and her pulse is 110 beats per minute. Which of the following substances would provide the fastest reversal of warfarin's effects?

A. Vitamin K (16%)
B. Protamine (2%)
C. Aminocaproic acid (1%)
D. Fresh frozen plasma (78%)
E. Cryoprecipitate (1%)
F. Desmopressin (0%)

Correct
78%
18 secs
01/30/2021

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Warfarin is the most commonly used agent for long-term anticoagulation in the setting of venous thromboses and pulmonary thromboembolism. Warfarin inhibits the vitamin K dependent g-carboxylation of the glutamic acid residues of clotting factors II, VII, IX and X, causing production of dysfunctional coagulation proteins.

The therapeutic effect of warfarin is monitored by measuring the prothrombin time (PT). The international normalized ratio (INR) is a standardized PT. The target INR for therapeutic warfarin anticoagulation is 2-3. Bleeding is a common complication of warfarin therapy and the risk is increased with INRs above 3.0. Treatment of life-threatening bleeding requires rapid reversal using fresh frozen plasma. Vitamin K can help to reverse warfarin action, but the effects take time.

(Choice B) Protamine is used for heparin reversal. It acts by binding and chemically inactivating heparin.

(Choice C) Aminocaproic acid is an antifibrinolytic agent that inhibits plasminogen activators and, to a lesser degree, antiplasmin activity. Aminocaproic acid helps achieve hemostasis when fibrinolysis is the cause of bleeding.

(Choice E) Whereas fresh frozen plasma contains all of the coagulation factors, cryoprecipitate contains only cold-soluble proteins (Factor VIII, fibrinogen, von Willebrand factor, and vitronectin).

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(Choice C) Aminocaproic acid is an antifibrinolytic agent that inhibits plasminogen activators and, to a lesser degree, antiplasmin activity. Aminocaproic acid helps achieve hemostasis when fibrinolysis is the cause of bleeding.

(Choice E) Whereas fresh frozen plasma contains all of the coagulation factors, cryoprecipitate contains only cold-soluble proteins (Factor VIII, fibrinogen, von Willebrand factor, and vitronectin).

(Choice F) Desmopressin is a synthetic analogue of anti-diuretic hormone (ADH) used in the treatment of diabetes insipidus. At high doses, desmopressin increases factor VIII activity in patients with hemophilia A and von Willebrand disease. High-dose desmopressin can help control bleeding associated with these disorders.

Educational Objective:
Both vitamin K and fresh frozen plasma are used for reversing warfarin-induced anticoagulation. Fresh frozen plasma rapidly reverses warfarin's effects whereas vitamin K requires time for clotting factor re-synthesis.

Pharmacology	Hematology & Oncology	Anticoagulants
Subject	System	Topic

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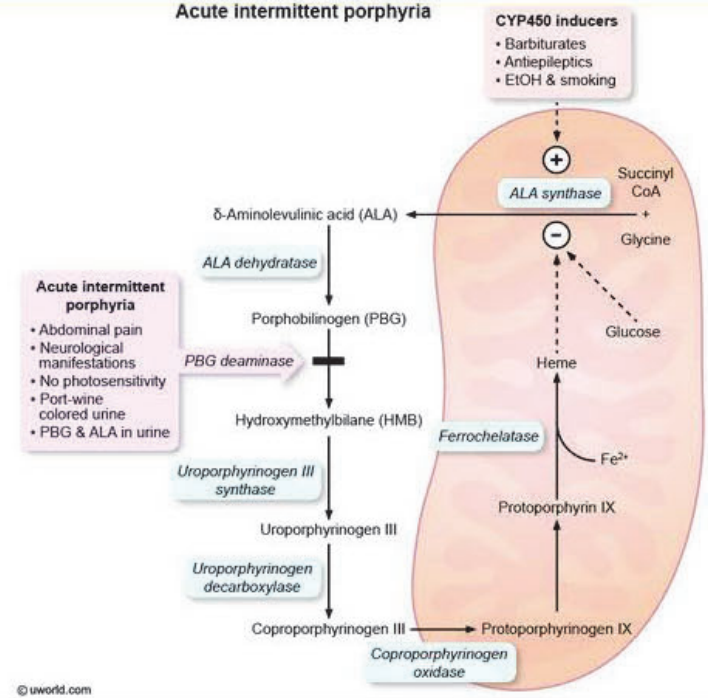
A 22-year-old woman comes to the hospital due to a 5-day history of nausea, constipation, and severe, poorly localized abdominal pain. She also reports anxiety, difficulty concentrating, poor sleep quality, and tingling of the limbs. The patient has had several similar episodes in the past. She does not take any medications or use tobacco, alcohol, or illicit drugs. The patient has been restricting her diet to lose weight. On examination, the abdomen is soft, nontender, and nondistended. Bowel sounds are decreased. The patient receives an intravenous infusion of a heme preparation that leads to rapid resolution of her symptoms. The improvement in symptoms is most likely due to treatment-induced downregulation of which of the following enzymes?

A. Aminolevulinate dehydratase (9%)
B. Aminolevulinate synthase (52%)
C. Bilirubin glucuronyl transferase (4%)
D. Ferrochelatase (12%)
E. Porphobilinogen deaminase (19%)

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This patient with neurologic symptoms (eg, tingling, difficulty concentrating) and recurrent episodes of nonspecific abdominal pain likely has **acute intermittent porphyria** (AIP), an autosomal dominant disease characterized by **porphobilinogen (PBG) deaminase** deficiency. Management of AIP attacks includes infusion of hemin, which downregulates hepatic **aminolevulinate (ALA) synthase** (rate-limiting enzyme in hepatic pathway of heme synthesis).

Heme, a porphyrin, is synthesized in the liver for use in the cytochrome p450 enzyme system and in the bone marrow for hemoglobin use (these 2 synthesis pathways are regulated differently). A deficiency in any of the enzymes responsible for porphyrin synthesis can result in porphyria. Clinical manifestations result from the accumulation of porphyrin precursors in blood, tissues, and urine. AIP attacks, which are characterized by acute abdominal pain and neurologic symptoms, are due to accumulation of **ALA** and **PBG**, generally resulting from a combination of 2 factors:

- PBG deaminase deficiency (inherited)
- ALA synthase induction, typically precipitated by certain medications (eg, phenobarbital, griseofulvin, phenytoin), alcohol use, smoking, progesterone (eg, puberty), or a low-calorie diet (as seen with this patient)

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patient)

Glucose or **hemin** inhibit ALA synthase and are used in AIP management. PBG deaminase deficiency by itself is generally not sufficient for development of AIP attacks (many patients with PBG deaminase deficiency are asymptomatic), and PBG deaminase enzyme activity is not directly affected by hemin infusion **(Choice E)**.

(Choices A and D) Deficiencies of ALA dehydratase and ferrochelatase (inhibited by lead) are seen with lead poisoning. Ferrochelatase deficiency is also seen with erythropoietic protoporphyria, characterized by cutaneous photosensitivity beginning in early childhood.

(Choice C) Bilirubin glucuronyl transferase is a hepatic enzyme that is responsible for the conjugation of bilirubin (byproduct of heme catabolism) with glucuronide, a polar molecule that improves bilirubin solubility for subsequent biliary excretion. A decrease in glucuronyl transferase activity results in unconjugated hyperbilirubinemia.

Educational objective:
Acute intermittent porphyria attacks are due to the accumulation of aminolevulinate (ALA) and porphobilinogen (PBG), resulting from inherited PBG deaminase deficiency combined with ALA synthase induction (typically due to certain medications, alcohol use, or a low-calorie diet). Management with

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(Choices A and D) Deficiencies of ALA dehydratase and ferrochelatase (inhibited by lead) are seen with lead poisoning. Ferrochelatase deficiency is also seen with erythropoietic protoporphyria, characterized by cutaneous photosensitivity beginning in early childhood.

(Choice C) Bilirubin glucuronyl transferase is a hepatic enzyme that is responsible for the conjugation of bilirubin (byproduct of heme catabolism) with glucuronide, a polar molecule that improves bilirubin solubility for subsequent biliary excretion. A decrease in glucuronyl transferase activity results in unconjugated hyperbilirubinemia.

Educational objective:
Acute intermittent porphyria attacks are due to the accumulation of aminolevulinate (ALA) and porphobilinogen (PBG), resulting from inherited PBG deaminase deficiency combined with ALA synthase induction (typically due to certain medications, alcohol use, or a low-calorie diet). Management with glucose or hemin inhibits ALA synthase activity.

Biochemistry	Hematology & Oncology	Heme metabolism
Subject	System	Topic

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A 72-year-old woman comes to the office for a routine follow-up appointment. She has no symptoms and her past medical history is insignificant. Her temperature is 36.7 C (98 F), blood pressure is 110/80 mm Hg, and pulse is 76/min and irregular. ECG shows atrial fibrillation with no ischemic changes. Anticoagulation therapy with warfarin is initiated for stroke prevention. Two days later, the patient is hospitalized with severe skin and subcutaneous fat necrosis. Drug effects on which of the following processes are most likely responsible for this patient's skin findings?

A. Factor IX synthesis (2%)
B. Factor VIIa activity (6%)
C. Factor XIa activity (0%)
D. Fibrinogen conversion (2%)
E. Protein C activity (83%)
F. Prothrombin conversion (2%)

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This patient has **warfarin-induced skin necrosis**, a rare but important complication of warfarin initiation. It is thought to be due to a **transient hypercoagulable state** that can occur during the **first few days** of warfarin therapy.

The overall anticoagulant effect of **warfarin** is due primarily to its inhibition of the vitamin K-dependent gamma-carboxylation of clotting factors II, VII, IX, and X ("vitamin K-dependent clotting factors"). However, warfarin also decreases carboxylation of proteins C and S, which normally exert an anticoagulant effect (through proteolysis and deactivation of factors V and VIII). **Protein C** has a **short half-life**, so its anticoagulant activity is reduced quickly when warfarin therapy is initiated, by about 50% within the first day. During this time, the vitamin K-dependent clotting factors II, IX, and X continue to exert a procoagulant effect as they have longer half-lives (factor VII has a short half-life similar to protein C).

This difference in half-lives translates into a transient hypercoagulable state:

- Decreased protein C (anticoagulant) activity → procoagulant effect
- Persistent clotting factor II, IX, and X activity → procoagulant effect

Thrombosis and clot can interrupt blood flow to the skin and lead to skin necrosis. For this reason, overlapping coadministration of heparin **("heparin bridge")** is commonly used when warfarin is initiated

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overlapping coadministration of heparin **("heparin bridge")** is commonly used when warfarin is initiated. The risk of warfarin-induced skin necrosis is increased in patients with a preexisting protein C deficiency, as well as in those started on a large loading dose of warfarin.

(Choice A) Warfarin affects coagulation factor carboxylation, not synthesis.

(Choice B) Factor VII inhibition by warfarin has an anticoagulant effect.

(Choice C) Warfarin does not have a major direct effect on factor XI activity that would cause skin necrosis.

(Choices D and F) Fibrinogen and prothrombin activity may be impacted downstream, but this is not the primary process affected by warfarin.

Educational objective:
Warfarin inhibits proteins C and S (natural anticoagulants present in blood), which can lead to skin necrosis, particularly in patients with protein C or S deficiency. This complication is usually seen in the first few days of warfarin therapy.

References

- Coumadin-induced skin necrosis in a 64 year-old female despite LMWH bridging therapy.

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A 44-year-old man who was recently diagnosed with idiopathic membranous nephropathy after developing edema comes to the office due to a sudden onset of left flank pain and gross hematuria. The patient has no other medical problems. He is taking furosemide and ramipril. Blood pressure is 135/85 mm Hg and pulse is 88/min. On examination, there is left flank tenderness. The patient's edema has improved from the previous visit. There is a left-sided varicocele that the patient has not noticed before. Urinalysis shows increased proteinuria and new hematuria. Serum lactate dehydrogenase is elevated. Urinary loss of which of the following substances most likely predisposed this patient to his acute condition?

A. Albumin (32%)
B. Alpha-1 antitrypsin (1%)
C. Antithrombin III (49%)
D. Ceruloplasmin (2%)
E. Immunoglobulins (10%)
F. Lipoproteins (3%)

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This patient with membranous nephropathy, flank pain, hematuria, and left varicocele likely has **renal vein thrombosis** (RVT) as a result of **nephrotic syndrome**. Due to increased glomerular capillary wall permeability in nephrotic syndrome, many important substances are lost in the urine, causing a number of complications. Loss of anticoagulant factors, especially **antithrombin III**, leads to a hypercoagulable state, of which RVT can be a manifestation. Patients with RVT can develop sudden-onset abdominal or **flank pain** and gross **hematuria** with **elevated lactate dehydrogenase** as a result of renal infarction.

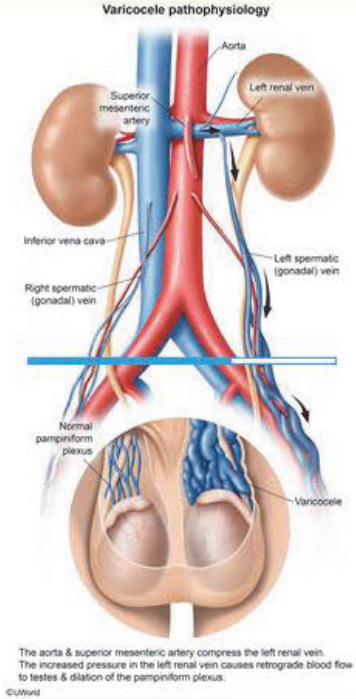
Left-sided varicoceles are relatively common in healthy pubertal men as the aorta and superior mesenteric artery can compress the left renal vein ("nutcracker effect"), resulting in increased intravascular pressure in the left gonadal vein with retrograde blood flow and varicocele formation. However, a new-onset left varicocele associated with ipsilateral flank pain and hematuria should raise suspicion for RVT causing impaired left gonadal venous drainage.

(Choice A) Albumin is also lost in massive quantities in urine in nephrotic syndrome, leading to hypoproteinemia, decreased intravascular oncotic pressure, and fluid shifts into the interstitium. Albuminuria explains the patient's edema (improved from his previous visit) but not his acute flank pain, hematuria, and left-sided varicocele, which are more likely due to thrombosis. Protein loss also results in a negative nitrogen balance.

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liver cirrhosis.

(Choice D) Serum ceruloplasmin is decreased in Wilson disease (hepatolenticular degeneration), which is clinically characterized by liver disease, motor abnormalities, and psychiatric symptoms. Ceruloplasmin has no role in the pathogenesis of nephrotic syndrome.

(Choice E) The loss of immunoglobulins and low-molecular-weight components of complement (such as factor B) makes patients with nephrotic syndrome vulnerable to infections, especially pneumococcal infections.

(Choice F) Lipiduria is common in nephrotic syndrome as a result of increased lipoprotein synthesis by the liver and increased glomerular capillary wall permeability, leading to lipid loss in the urine in the form of free fat and oval fat bodies (with characteristic Maltese cross appearance under polarized light). However, lipiduria does not contribute to the hypercoagulable state.

Educational objective:
Nephrotic syndrome is a hypercoagulable state. Sudden-onset abdominal or flank pain, hematuria, and left-sided varicoceles suggest renal vein thrombosis, a well-known complication of nephrotic syndrome. Loss of anticoagulant factors, especially antithrombin III, is responsible for the thrombotic and thromboembolic complications of nephrotic syndrome.

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A 20-year-old man is brought to the emergency department due to fever, headache, and neck pain for the last day. He has no significant medical history. Temperature is 38.7 C (101.7 F), blood pressure is 120/72 mm Hg, pulse is 112/min, and respirations are 26/min. There is neck stiffness and a petechial rash on the trunk. Cerebrospinal fluid (CSF) analysis reveals the following:

Glucose	30 mg/dL
Protein	180 mg/dL
Leukocytes	1,500/mm^3
Neutrophils	70%

CSF gram stain shows gram-negative diplococci. In the emergency department, the patient's hemodynamic status deteriorates rapidly. Blood pressure drops to 80/50 mm Hg, and the venous access sites are oozing blood. Which of the following findings is most likely to be seen on this patient's peripheral blood smear?

A. ~~Atypical lymphocytosis~~ (2%)

B. Howell-Jolly bodies (5%)

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CSF gram stain shows gram-negative diplococci. In the emergency department, the patient's hemodynamic status deteriorates rapidly. Blood pressure drops to 80/50 mm Hg, and the venous access sites are oozing blood. Which of the following findings is most likely to be seen on this patient's peripheral blood smear?

A. ~~Atypical lymphocytosis~~ (2%)
B. ~~Howell-Jolly bodies~~ (5%)
C. Hypersegmented neutrophils (2%)
D. Reactive thrombocytosis (16%)
E. Schistocytes (61%)
F. Severe pancytopenia (11%)

Correct

61%
Answered correctly

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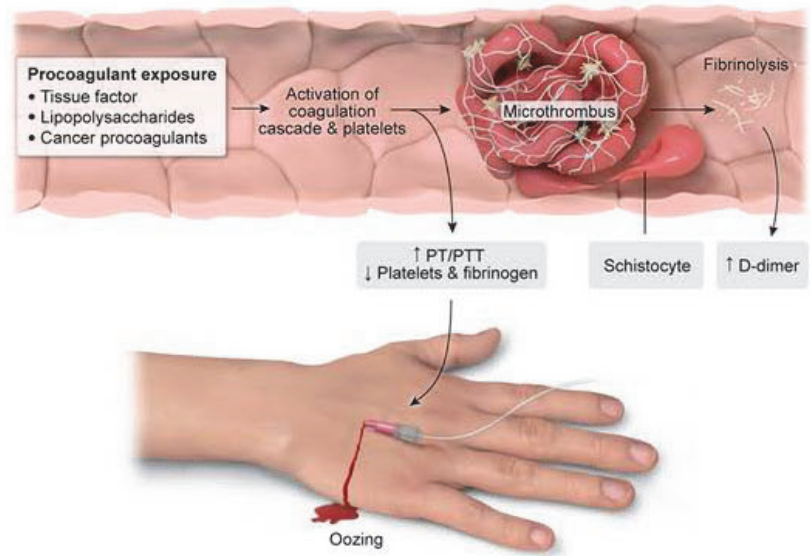
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Acute disseminated intravascular coagulation



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This patient's clinical findings (fever, headache, neck stiffness, rash) and cerebrospinal fluid analysis (elevated protein, low glucose, leukocytosis, gram-negative diplococci) are indicative of **meningococcal meningitis**; he subsequently developed septic shock (severe hypotension) while in the emergency department. His **bleeding** from venous puncture sites is highly suggestive of **disseminated intravascular coagulation** (DIC), a consumptive coagulopathy associated with **sepsis**, malignancy, trauma, and obstetric complications.

In DIC due to gram-negative sepsis, the coagulation cascade is activated by bacterial **endotoxins**, leading to widespread fibrin deposition and the consumption of coagulation factors and platelets, with eventual bleeding. Deposition of fibrin strands in small vessels can cause shearing of circulating erythrocytes, resulting in schistocytes (fragmented erythrocytes) on peripheral smear. Laboratory values in DIC typically show **decreased platelet count** and fibrinogen level and **prolonged PT and PTT** (indicating a consumption of coagulation factors).

(Choice A) Atypical lymphocytes are reactive lymphocytes with abundant, pale-blue cytoplasm and large nuclei. They are often seen in viral infections, particularly infectious mononucleosis.

(Choice B) Howell-Jolly bodies are round, dark, purple/red inclusions within erythrocytes. These

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bleeding. Deposition of fibrin strands in small vessels can cause shearing of circulating erythrocytes, resulting in schistocytes (fragmented erythrocytes) on peripheral smear. Laboratory values in DIC typically show **decreased platelet count** and fibrinogen level and **prolonged PT and PTT** (indicating a consumption of coagulation factors).

(Choice A) Atypical lymphocytes are reactive lymphocytes with abundant, pale-blue cytoplasm and large nuclei. They are often seen in viral infections, particularly infectious mononucleosis.

(Choice B) Howell-Jolly bodies are round, dark, purple/red inclusions within erythrocytes. These represent nuclear fragments that are typically removed by the spleen; they can be seen in patients with splenectomy or reduced splenic function (eg, sickle cell).

(Choice C) Hypersegmented neutrophils are characterized by nuclei with ≥6 lobes. They are a feature of megaloblastic anemia (vitamin B_{12} or folate deficiency).

(Choice D) Reactive thrombocytosis is common in infection due to cytokine-mediated megakaryocyte proliferation and the release of platelets into the peripheral bloodstream. In contrast, patients with DIC have thrombocytopenia due to platelet consumption.

(Choice F) Severe pancytopenia is often seen in patients with aplastic anemia, which is characterized by destruction of hematopoietic stem cells and profoundly hypocellular bone marrow. Although patients with

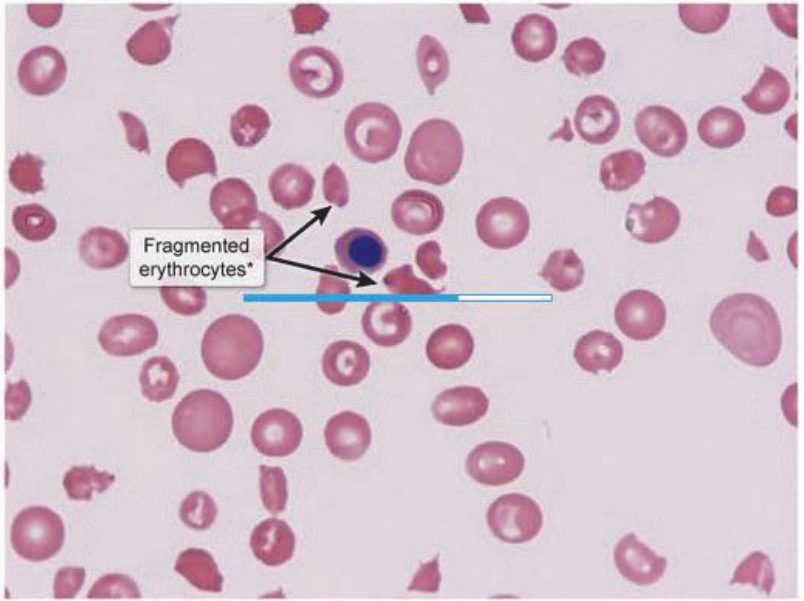
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bleeding. Deposition of fibrin strands in small vessels can cause shearing of circulating erythrocytes.

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Schistocytes



*Associated with microangiopathic hemolytic anemia and prosthetic cardiac valves

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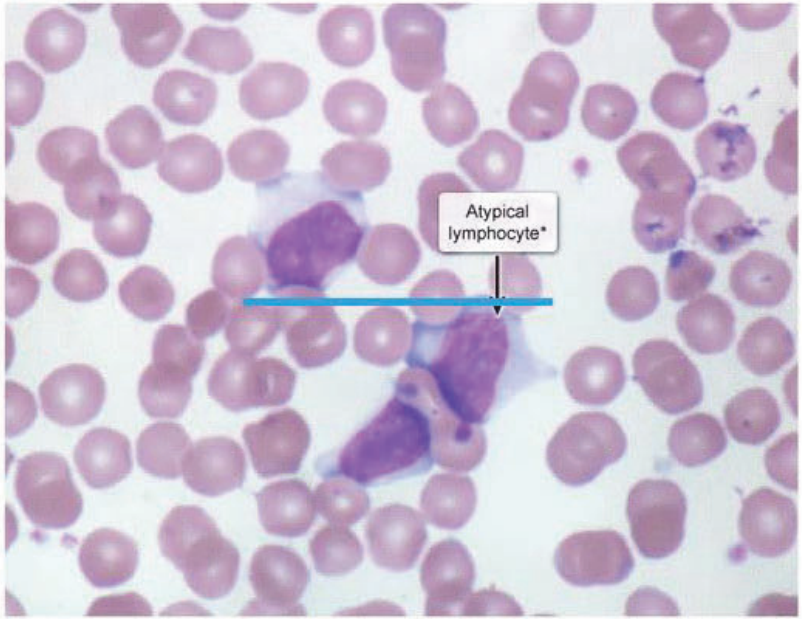
destruction of hematopoietic stem cells and profoundly hypocellular bone marrow. Although patients with

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bleeding. Deposition of fibrin strands in small vessels can cause shearing of circulating erythrocytes.

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Atypical lymphocytes



*Large reactive lymphocyte with abundant blue cytoplasm

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destruction of hematopoietic stem cells and profoundly hypocellular bone marrow. Although patients with

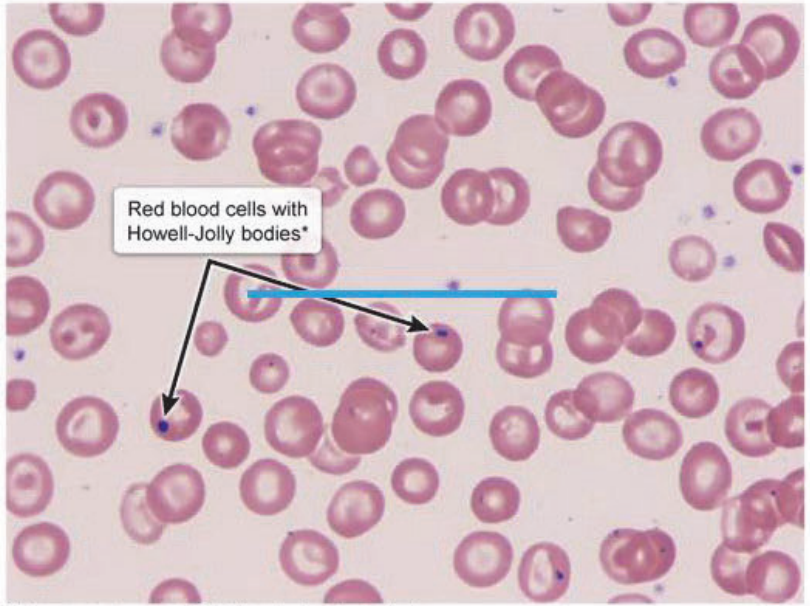
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bleeding. Deposition of fibrin strands in small vessels can cause shearing of circulating erythrocytes.

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Howell-Jolly bodies



*Nuclear remnants associated with asplenia or hyposplenia

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destruction of hematopoietic stem cells and profoundly hypocellular bone marrow. Although patients with

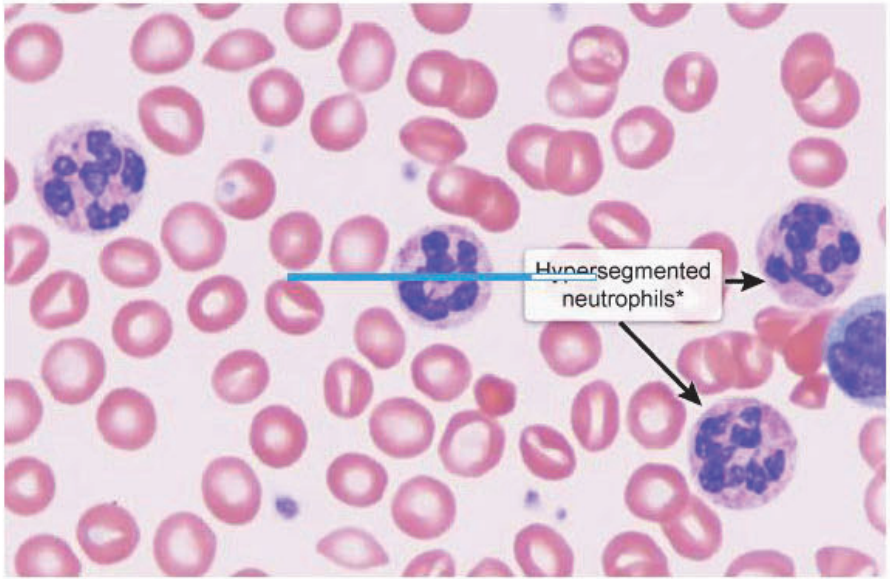
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bleeding. Deposition of fibrin strands in small vessels can cause shearing of circulating erythrocytes.

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Megaloblastic anemia



* ≥6 nuclear lobes

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destruction of hematopoietic stem cells and profoundly hypocellular bone marrow. Although patients with

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megaloblastic anemia (vitamin B_{12} or folate deficiency).

(Choice D) Reactive thrombocytosis is common in infection due to cytokine-mediated megakaryocyte proliferation and the release of platelets into the peripheral bloodstream. In contrast, patients with DIC have thrombocytopenia due to platelet consumption.

(Choice F) Severe pancytopenia is often seen in patients with aplastic anemia, which is characterized by destruction of hematopoietic stem cells and profoundly hypocellular bone marrow. Although patients with severe pancytopenia are at risk for bleeding, oozing from venipuncture sites in the setting of sepsis almost always indicates DIC.

Educational objective:
Disseminated intravascular coagulation is a common complication of gram-negative bacterial sepsis due to activation of the coagulation cascade by bacterial endotoxins, which leads to the formation of microthrombi. Peripheral smear shows fragmented erythrocytes (schistocytes) and thrombocytopenia. Laboratory tests show decreased fibrinogen levels and prolonged PT and PTT.

Pathology	Hematology & Oncology	DIC
Subject	System	Topic

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A 12-year-old boy experiences excessive bleeding following a tooth extraction. His past medical history includes episodes of painful joint swelling from minor trauma. Physical examination shows a soft and nontender abdomen with a liver span of 10 cm. The spleen is not palpable. Laboratory results are as follows:

Bleeding time	5 min
Activated partial thromboplastin time	25 sec
Prothrombin time	23 sec

This patient most likely has a deficiency involving which of the following factors?

- A. Factor VII (59%)
- B. ~~Factor VIII~~ (22%)
- C. ~~Factor XI~~ (2%)

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Activated partial thromboplastin time	25 sec
Prothrombin time	23 sec

This patient most likely has a deficiency involving which of the following factors?

- A. Factor VII (59%)
- B. ~~Factor VIII~~ (22%)
- C. ~~Factor XI~~ (2%)
- D. ~~Hageman factor~~ (2%)
- E. von Willebrand factor (13%)

Correct

59% Answered correctly

02 mins, 12 secs Time Spent

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(Choice C) Factor XI deficiency results in a rare autosomal recessive disorder called hemophilia C. Spontaneous bleeding is rare in this condition, but affected patients are at increased risk for bleeding following surgery or trauma. Coagulation studies will show a prolonged aPTT and normal PT.

(Choice D) Hageman factor (factor XII) deficiency is an autosomal recessive disorder that does not typically cause clinically significant bleeding despite aPTT prolongation.

(Choice E) von Willebrand factor (vWF) functions as both a carrier molecule for factor VIII (protecting it from being degraded) and as a mediator of platelet adhesion to the endothelium. It presents with prolonged bleeding time and normal/prolonged aPTT.

Educational objective:
A normal bleeding time indicates adequate platelet hemostatic function. A normal activated partial thromboplastin time (aPTT) indicates an intact intrinsic coagulation system. Prolonged prothrombin time in the setting of normal aPTT indicates a defect in the extrinsic coagulation system at a step that is not shared with the intrinsic system.

Pathophysiology	Hematology & Oncology	Coagulopathy
Subject	System	Topic

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A 72-year-old man is brought into the hospital by paramedics after he was found disoriented and wandering in the street. He has a past medical history of dementia, hypertension, and stroke. Physical examination reveals a disoriented, thin-appearing male. His gingivae are swollen and bleed easily. Ecchymoses are noted on his legs. The laboratory values are provided below:

Hemoglobin	9.6 g/dL
Platelets	152,000/mm^3
White blood cell count	4,500/mm^3
Blood urea nitrogen	28 mg/dL
Serum creatinine	0.8 mg/dL
Prothrombin time	11 sec
Partial thromboplastin time	30 sec

Which of the following is most likely responsible for this patient's ecchymoses?

A. Platelet dysfunction (14%)

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Prothrombin time	11 sec
Partial thromboplastin time	30 sec

Which of the following is most likely responsible for this patient's ecchymoses?

A. ~~Platelet dysfunction~~ (14%)

B. ~~Endothelial cell dysfunction~~ (3%)

C. ~~Hepatic dysfunction~~ (4%)

✓ D. Water soluble vitamin deficiency (64%)

E. ~~Fat soluble vitamin deficiency~~ (9%)

F. ~~Zinc deficiency~~ (3%)

Correct

64% Answered correctly

01 min, 46 secs Time Spent

09/25/2020 Last Updated

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Vitamin C (ascorbic acid) is a water soluble vitamin that functions as a cofactor in numerous biochemical processes, including collagen synthesis. Deficiency in vitamin C ("scurvy") is most commonly due to insufficient intake, which tends to occur in the setting of chronic drug or alcohol abuse, malnourishment, or old age.

Cutaneous signs of scurvy include phrynoderma (perifollicular hyperkeratosis), coiled hair, and poor wound healing. Mucosal findings include **bleeding gums** and loose teeth. Hemorrhagic complications include ecchymoses and petechiae, hemarthrosis, intramuscular bleeding, and bleeding within the central nervous system, gastrointestinal tract, and genitourinary system. Normocytic, normochromic anemia is typical, while **coagulation studies** (including PT and PTT) are **normal**. Treatment is with vitamin C supplementation, and symptomatic improvement is expected within days.

(Choice A) Common causes of platelet dysfunction in the elderly include uremia and NSAID use. This patient has mild dehydration and prerenal azotemia, which should not cause platelet dysfunction. Similarly, while this patient might be taking aspirin because of his stroke history, aspirin alone would not cause bleeding gums.

(Choice B) Endothelial cell dysfunction can cause von Willebrand disease. However, this condition typically presents earlier in life and is associated with a prolonged PTT.

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patient has mild dehydration and prerenal azotemia, which should not cause platelet dysfunction. Similarly, while this patient might be taking aspirin because of his stroke history, aspirin alone would not cause bleeding gums.

(Choice B) Endothelial cell dysfunction can cause von Willebrand disease. However, this condition typically presents earlier in life and is associated with a prolonged PTT.

(Choice C) Hepatic dysfunction can cause prolongation of both PT and PTT or prolongation of PT with a normal PTT. This patient has a normal PT and PTT.

(Choice E) Deficiency in vitamin K (a fat soluble vitamin) results in a prolonged PT.

(Choice F) Zinc deficiency is characterized by an erosive dermatitis of the hands and feet and the perioral, perianal and periocular regions. Other findings include diarrhea, conjunctivitis, and impaired wound healing.

Educational objective:
Vitamin C deficiency (scurvy) is associated with coiled hair, perifollicular keratosis, hemorrhage, easy bruising, bleeding gums, and loose teeth. The PT, PTT, and platelet count are normal.

Pathology Hematology & Oncology Vitamin C deficiency

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A 50-year-old woman with a history of systemic lupus erythematosus is admitted with fever, chills, vomiting, and burning pain when urinating. Temperature is 39.3 C (102.7 F), blood pressure is 80/50 mm Hg, pulse is 120/min, and respirations are 20/min. On examination, costovertebral angle tenderness is present. The patient is given intravenous antibiotics. Over the next several hours, she has decreased urine output despite aggressive intravenous hydration. Blood is oozing around the central venous catheter. Laboratory results are as follows:

Complete blood count	
Hemoglobin	9.0 g/dL
Platelets	68,000/mm^3
Leukocytes	24,500/mm^3
Coagulation studies	
Prothrombin time	23 sec
Partial thromboplastin time	60 sec
Plasma fibrinogen	100 mg/dL (150-350)

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Platelets	88,000/mm³
Leukocytes	24,500/mm³
Coagulation studies	
Prothrombin time	23 sec
Partial thromboplastin time	60 sec
Plasma fibrinogen	100 mg/dL (150-350)

Which of the following is the most likely cause of this patient's hematologic abnormalities?

A. Accumulation of anticardiolipin antibodies (8%)

B. Accumulation of ultra-large von Willebrand factor multimers (3%)

C. Consumptive coagulopathy (73%)

D. ~~Immune-mediated platelet destruction~~ (11%)

E. ~~Impaired hepatic synthetic activity~~ (2%)

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Laboratory characteristics of coagulopathies

	Platelet count	Prothrombin time	Partial thromboplastin time	Plasma fibrinogen values	Peripheral blood smear
von Willebrand disease	Normal	Normal	↑	Normal	Normal
Immune thrombocytopenic purpura	↓	Normal	Normal	Normal	Isolated thrombocytopenia
TTP-HUS	↓	Normal	Normal	Normal	RBC fragmentation
Disseminated intravascular coagulation	↓	↑	↑	↓	RBC fragmentation

HUS = hemolytic uremic syndrome; **RBC** = red blood cell; **TTP** = thrombotic thrombocytopenic purpura.

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HUS = hemolytic uremic syndrome; **RBC** = red blood cell; **TTP** = thrombotic thrombocytopenic purpura.

This patient's costovertebral angle tenderness, dysuria, and leukocytosis are indicative of acute pyelonephritis complicated by septic shock (hypotension, tachycardia). Her laboratory results show a consumptive coagulopathy (thrombocytopenia, prolonged PT/PTT, low fibrinogen), which, along with bleeding from the central catheter site, are likely due to **disseminated intravascular coagulation** (DIC).

DIC is a common complication of **sepsis** (particularly with gram-negative organisms) because **lipopolysaccharide** is a **procoagulant** that triggers the coagulation cascade. This leads to the formation of fibrin- and platelet-rich thrombi in the vasculature, which consumes platelets **(thrombocytopenia)**, coagulation factors **(prolonged PT/PTT)**, and fibrinogen. Fibrinolysis is then triggered to degrade the clots, which **elevates D-dimer** (a fibrin degradation product) and depletes protein C, protein S, and antithrombin. The thrombi also often shear red blood cells, leading to **microangiopathic hemolytic anemia** (MAHA).

Most patients with acute DIC have signs of bleeding, such as **oozing from vascular catheters**, mucocutaneous bleeding, ecchymosis, or petechiae. End organ damage (eg, renal insufficiency, pulmonary hemorrhage) is also common.

(Choice A) Anticardiolipin antibody is antiphospholipid antibody often seen in patients with lupus erythematosus. It can cause antiphospholipid antibody syndrome, which is marked by thromboembolism

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pulmonary hemorrhage) is also common.

(Choice A) Anticardiolipin antibody is antiphospholipid antibody often seen in patients with lupus erythematosus. It can cause antiphospholipid antibody syndrome, which is marked by thromboembolism and fetal loss (not bleeding). Although patients often have prolonged PTT (because the antiphospholipid interferes with the PTT test), PT is normal.

(Choice B) Thrombotic thrombocytopenic purpura (TTP) is caused by reduced activity of von Willebrand factor–cleaving protein ADAMTS13, leading to the accumulation of ultra-large von Willebrand factor multimers that trap platelets and generate platelet-rich thrombi in the microvasculature. Although patients usually develop thrombocytopenia, MAHA, fever, confusion, and organ damage (eg, acute renal failure), the coagulation cascade is unaffected; therefore, PT/PTT and fibrinolysis (fibrinogen level) are normal, and bleeding does not occur.

(Choice D) Immune (idiopathic) thrombocytopenic purpura (ITP) is marked by autoantibodies to platelets/megakaryocytes; thrombocytopenia is the only peripheral blood abnormality. Coagulation studies (eg, PT, PTT) and fibrinogen levels are normal. Spontaneous bleeding is very uncommon unless the platelet count is <10,000/mm^3.

(Choice E) The liver generates thrombopoietin and the majority of clotting factors. Therefore, patients with

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bleeding does not occur.

(Choice D) Immune (idiopathic) thrombocytopenic purpura (ITP) is marked by autoantibodies to platelets/megakaryocytes; thrombocytopenia is the only peripheral blood abnormality. Coagulation studies (eg, PT, PTT) and fibrinogen levels are normal. Spontaneous bleeding is very uncommon unless the platelet count is <10,000/mm^3.

(Choice E) The liver generates thrombopoietin and the majority of clotting factors. Therefore, patients with significantly impaired hepatic function (eg, cirrhosis) sometimes have mild thrombocytopenia and prolonged coagulation studies. However, fibrinogen level is usually normal and this patient has no other signs of advanced hepatic dysfunction (eg, ascites, jaundice).

Educational objective:
Disseminated intravascular coagulation commonly occurs in the setting of sepsis and is characterized by widespread activation of the coagulation cascade with formation of microthrombi. Laboratory results reveal prolonged PT/PTT, thrombocytopenia, and low fibrinogen (ie, a consumptive coagulopathy), and patients usually have signs of bleeding (eg, oozing from venipuncture sites).

Pathology	Hematology & Oncology	DIC
Subject	System	Topic

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Pathology	Hematology & Oncology	DIC
Subject	System	Topic

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A 40-year-old man with end-stage renal disease due to type 1 diabetes mellitus is hospitalized for initiation of hemodialysis. A tunneled dialysis catheter is inserted into the right internal jugular vein. Before he is able to undergo dialysis treatment, the patient develops bleeding around the catheter exit site that is difficult to control. He has not been treated recently with anticoagulants. Further evaluation of this patient would most likely show which of the following laboratory abnormalities?

	Prothrombin time	Activated partial thromboplastin time	Platelet count	Bleeding Time	
✓ A. Normal	Normal	Normal	Prolonged	(29%)
B. Normal	Prolonged	Normal	Prolonged	(15%)
C. Normal	Prolonged	Normal	Normal	(8%)
D. Prolonged	Prolonged	Decreased	Prolonged	(34%)
E. Prolonged	Prolonged	Normal	Normal	(12%)

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Laboratory characteristics of coagulopathies

	PT	aPTT	Platelet count	Bleeding time
Hemophilia A & B	Normal	↑	Normal	Normal
von Willebrand factor deficiency	Normal	Normal or ↑	Normal	↑
Disseminated intravascular coagulation	↑	↑	↓	↑
Uremic platelet dysfunction	Normal	Normal	Normal	↑
Heparin administration	Normal	↑	Normal (except in heparin-induced thrombocytopenia)	Normal
Warfarin use	↑	↑ (weak effect)	Normal	Normal
Immune thrombocytopenia	Normal	Normal	↓	↑

aPTT = activated partial thromboplastin time; PT = prothrombin time.

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Excessive bleeding is common in patients with significant renal dysfunction due in part to the accumulation of **uremic toxins** in the circulation. These toxins impair platelet aggregation and adhesion, resulting in a **qualitative platelet disorder** characterized by **prolonged bleeding time** with normal platelet count, prothrombin time (PT), and activated partial thromboplastin time (aPTT). Uremic bleeding can be improved with **dialysis** as it removes the toxins and partially reverses the bleeding abnormality.

(Choice B) von Willebrand factor (vWF) acts as a bridge between glycoprotein 1b receptors and subendothelial collagen, allowing platelets to bind to damaged vessels. vWF deficiency results in platelet dysfunction with a prolonged bleeding time and normal platelet count. Since vWF also protects factor VIII from degradation, vWF deficiency can result in decreased factor VIII and prolonged aPTT.

(Choice C) Isolated aPTT prolongation is seen with hemophilia A, an X-linked disorder caused by factor VIII deficiency. Heparin use also prolongs the aPTT via antithrombin-associated inhibition of factors II and X (PT is usually normal due to the addition of heparin neutralizers in the PT reagent).

(Choice D) Disseminated intravascular coagulation is a consumptive coagulopathy associated with decreased platelet count and increased bleeding time, aPTT, and PT.

(Choice E) Warfarin inhibits vitamin K-dependent clotting factors (II, VII, IX, and X). Warfarin prolongs both PT and aPTT, but PT is increased much more than aPTT. Platelet count and bleeding time are

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dysfunction with a prolonged bleeding time and normal platelet count. Since vWF also protects factor VIII from degradation, vWF deficiency can result in decreased factor VIII and prolonged aPTT.

(Choice C) Isolated aPTT prolongation is seen with hemophilia A, an X-linked disorder caused by factor VIII deficiency. Heparin use also prolongs the aPTT via antithrombin-associated inhibition of factors II and X (PT is usually normal due to the addition of heparin neutralizers in the PT reagent).

(Choice D) Disseminated intravascular coagulation is a consumptive coagulopathy associated with decreased platelet count and increased bleeding time, aPTT, and PT.

(Choice E) Warfarin inhibits vitamin K-dependent clotting factors (II, VII, IX, and X). Warfarin prolongs both PT and aPTT, but PT is increased much more than aPTT. Platelet count and bleeding time are normal.

Education objective:
Abnormal bleeding in patients with uremia is due to a qualitative platelet disorder that causes prolonged bleeding time with normal platelet count, prothrombin time, and activated partial thromboplastin time.

References

- Coagulation assays and anticoagulant monitoring.

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A 24-year-old woman, gravida 1 para 0, at 28 weeks gestation comes to the labor and delivery unit due to intense abdominal pain, vaginal bleeding, and absent fetal movement. Temperature is 36.7 C (98.1 F), blood pressure is 170/96 mm Hg, pulse is 108/min, and respirations are 22/min. Pulse oximetry shows 98% on room air. Physical examination shows a tense abdomen and a firm, tender uterus. Ultrasound shows a hematoma between the placenta and the uterine wall and no fetal cardiac activity. Laboratory results are as follows:

Hemoglobin	9.2 g/dL
Platelets	60,000/mm^3
Aspartate aminotransferase (SGOT)	12 U/L
Alanine aminotransferase (SGPT)	24 U/L

The patient is hospitalized for further management. Once hospitalized, she begins to experience bleeding from her gums and intravenous catheter sites. Blood is also noted in the urinary catheter. Vital signs are unchanged, and she reports no shortness of breath. Which of the following is the most likely underlying cause of this patient's hospital symptoms?

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The patient is hospitalized for further management. Once hospitalized, she begins to experience bleeding from her gums and intravenous catheter sites. Blood is also noted in the urinary catheter. Vital signs are unchanged, and she reports no shortness of breath. Which of the following is the most likely underlying cause of this patient's hospital symptoms?

A. ~~Embolization of amniotic fluid into the maternal circulation~~ (24%)

B. Ascending polymicrobial infection of the endometrial lining (1%)

✓ C. Decidual tissue factor release into the maternal circulation (61%)

D. ~~Hepatic fatty infiltration with decreased clotting factor production~~ (7%)

E. ~~Complete rupture of the endometrium, myometrium, and serosa~~ (4%)

Correct

61% Answered correctly

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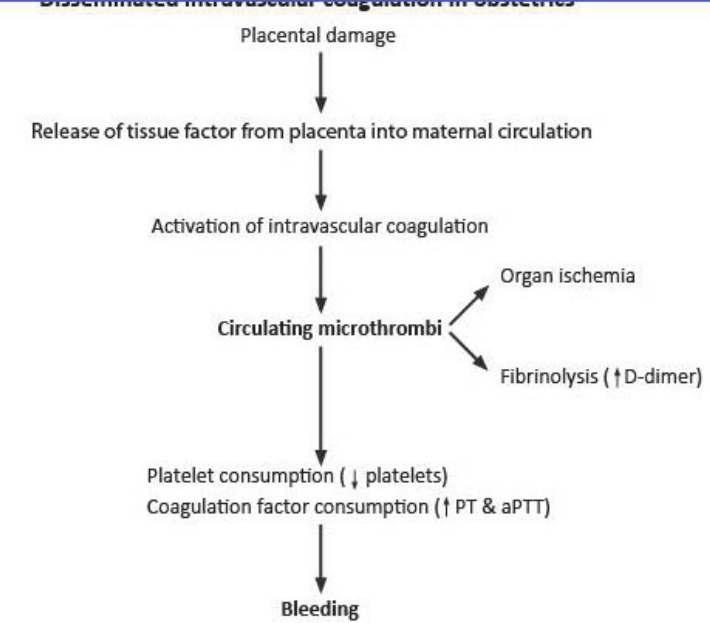
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Explanation

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Explanation

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PT = prothrombin time; aPTT = activated partial thromboplastin time.

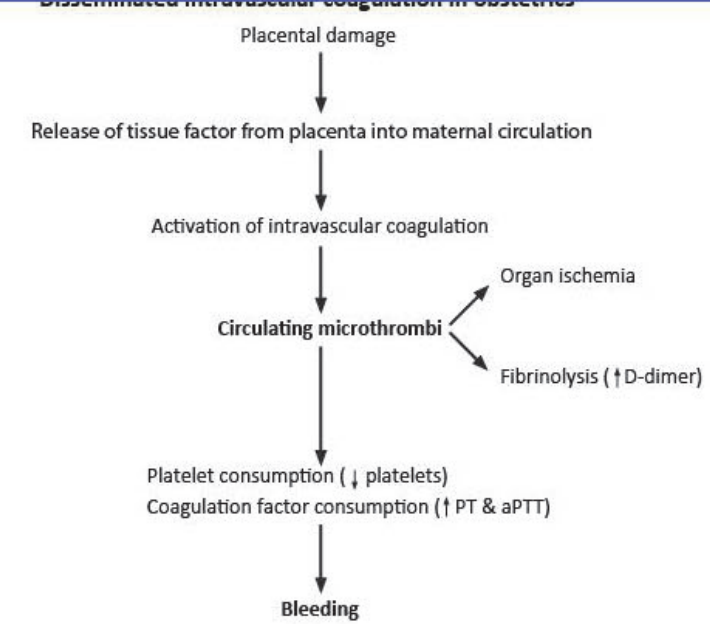
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Explanation

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PT = prothrombin time; aPTT = activated partial thromboplastin time.

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This pregnant patient with new bleeding from the gums and catheter sites likely has **disseminated intravascular coagulation (DIC)**, a life-threatening complication that can occur with postpartum hemorrhage, abruptio placentae, or amniotic fluid embolism. This patient has DIC due to **abruptio placentae** (ie, placental bleeding between the uterine wall and placenta), which results in premature placental separation, fetal hypoxia, and in severe cases, **fetal demise**. Patients with abruptio placentae typically have vaginal bleeding, uterine rigidity and/or tenderness, and contractions. Maternal hypertension (eg, preeclampsia) and tobacco use are risk factors.

Severe placental abruption (eg, retroplacental hematoma) causes **decidual damage and ischemia**, thereby triggering **tissue factor release** into the maternal circulation. Tissue factor, a procoagulant, then activates the extrinsic pathway of the coagulation cascade to cause excessive thrombin generation with formation of circulating platelet-fibrin microthrombi. As clotting factors and platelets are rapidly consumed, a consumptive coagulopathy (eg, **thrombocytopenia**, prolonged PT & aPTT) develops that results in profound bleeding, classically from mucosal surfaces and intravenous line sites.

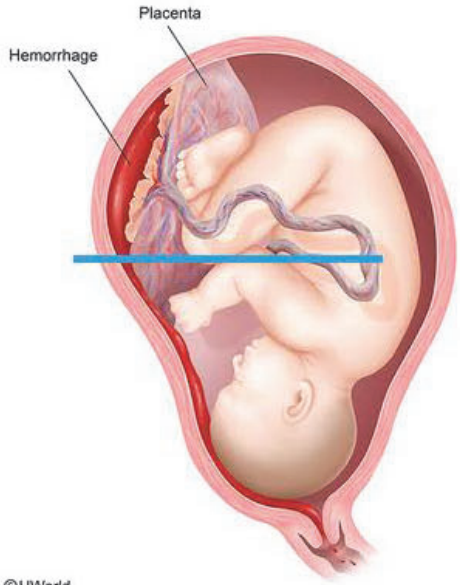
(Choice A) Amniotic fluid embolism (AFE) introduces fetal antigens and tissue factor from the amniotic fluid into the maternal circulation, triggering a massive immune response and increased release of procoagulant factors that can lead to DIC. However, AFE typically causes maternal circulatory collapse

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Placental abruption



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procoagulant factors that can lead to DIC. However, AFE typically causes maternal circulatory collapse

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(Choice B) An ascending polymicrobial infection of the endometrial lining (eg, postpartum endometritis) can cause uterine tenderness, vaginal bleeding, and sepsis, thereby precipitating DIC. However, patients typically also have fever and hypotension.

(Choice D) Acute fatty liver of pregnancy, characterized by microvesicular fatty infiltration of hepatocytes, can impair maternal hepatic function, reducing production of clotting factors and impairing clearance of fibrin degradation products, which may result in DIC. However, patients typically have elevated liver transaminases.

(Choice E) Complete uterine rupture through the endometrium, myometrium, and serosa can cause vaginal bleeding, abdominal pain, and fetal compromise. However, patients usually have had a prior uterine surgery and present with palpable fetal parts protruding through the disrupted uterine wall rather than a firm, tense uterus.

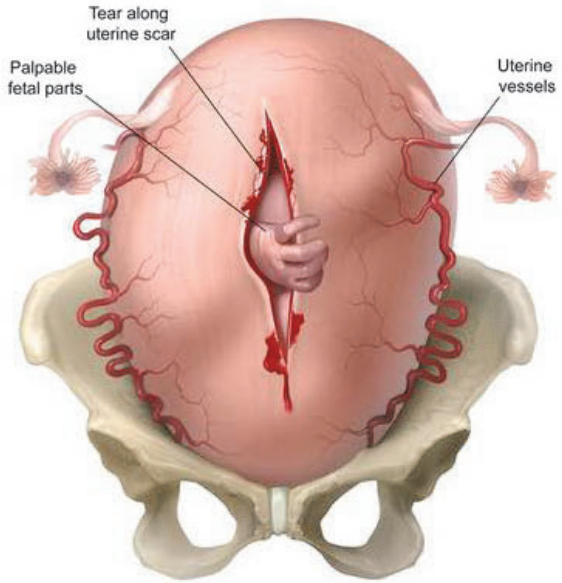
Educational objective:
Disseminated intravascular coagulation (DIC) can occur with abruptio placentae due to release of tissue factor, a procoagulant that activates the coagulation cascade, from the damaged decidua into the maternal circulation. DIC classically presents with thrombocytopenia and bleeding from mucosal surfaces (eg, gums) and intravenous line sites.

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Uterine rupture



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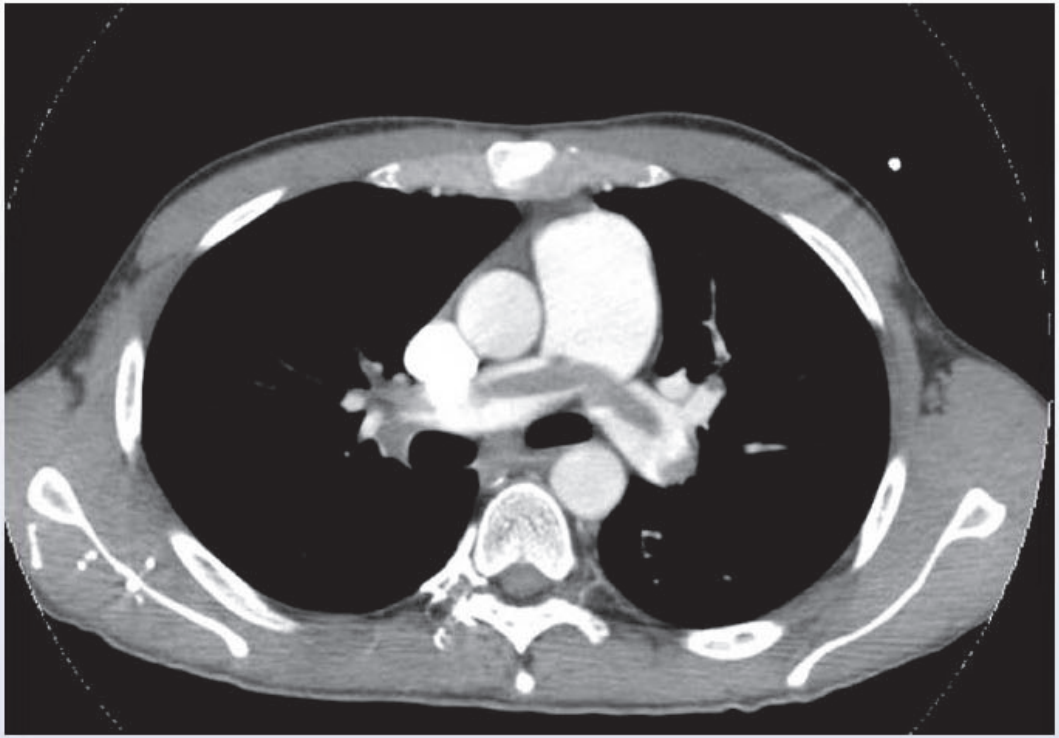
A 72-year-old man comes to the emergency department due to severe chest tightness and dyspnea that started 20 minutes ago at a family dinner. He has never experienced similar symptoms before. The patient's medical conditions include hypertension, hyperlipidemia, type 2 diabetes mellitus, and prostate cancer. He takes multiple medications and has no drug allergies. The patient smoked a pack of cigarettes daily for 30 years and stopped smoking 10 years ago. Chest CT scan with contrast is shown in the image below.



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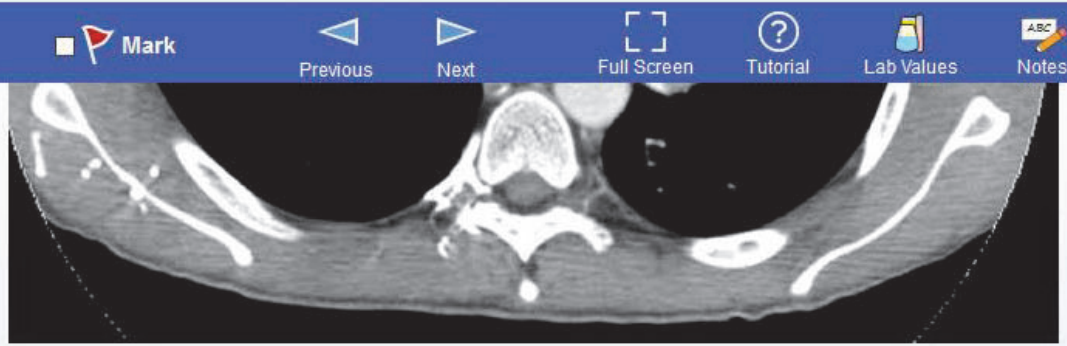
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below:



Which of the following factors most likely contributed to this patient's current condition?

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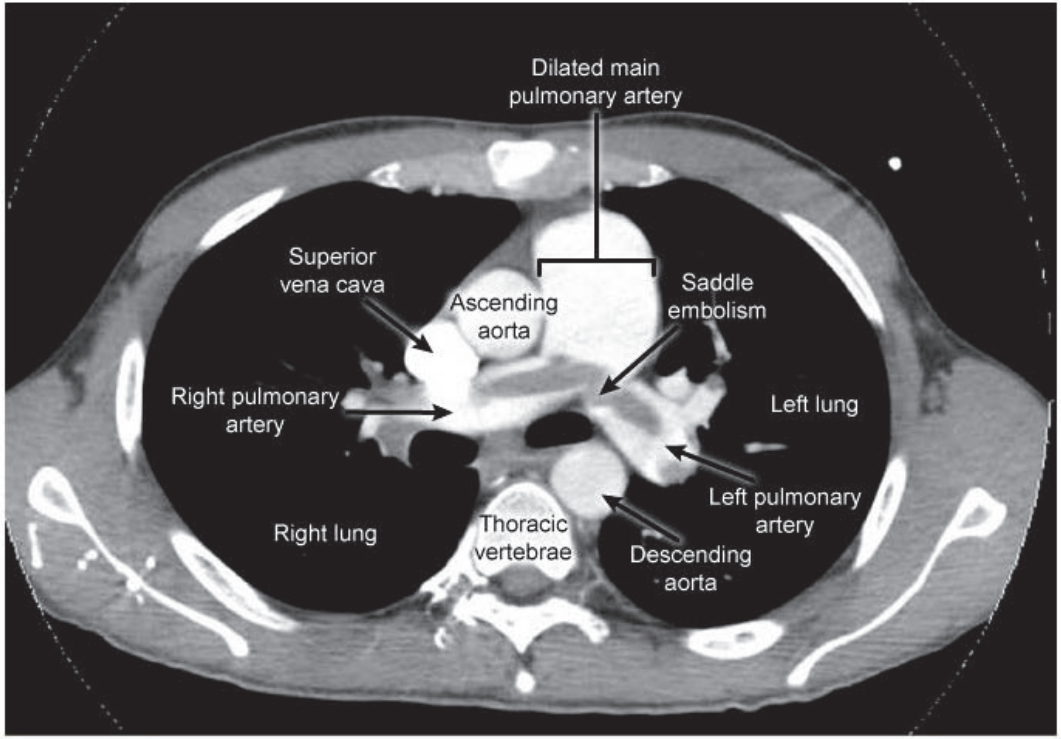
Which of the following factors most likely contributed to this patient's current condition?

- A. ~~Atherosclerosis~~ (18%)
- B. ~~Fluid overload~~ (1%)
- ✓ C. Hypercoagulability (63%)
- D. ~~Intimal tear~~ (11%)
- E. ~~Noninfectious vasculitis~~ (0%)
- F. ~~Pulmonary blob rupture~~ (2%)
- G. ~~Pulmonary metastasis~~ (1%)

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Saddle pulmonary embolism



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This patient is experiencing sudden-onset chest tightness and dyspnea, and CT scan of the chest shows a **saddle pulmonary embolism** (PE) straddling the bifurcation of the main pulmonary artery. The main pulmonary artery, usually comparable in diameter to the ascending aorta, is significantly dilated due to the proximal increase in hydrostatic pressure from the PE. Saddle PE can result in sudden cardiac death or severe hypotension, but many patients can be hemodynamically stable on presentation.

Venous thromboembolism (VTE) (ie, PE or deep venous thrombosis) results from the Virchow triad of endothelial injury, venous stasis, and a **hypercoagulable** state. **Malignancy** (eg, prostate cancer) induces a hypercoagulable state and is a strong risk factor for VTE. Active **smoking** is also a risk factor as it contributes to endothelial injury and a hypercoagulable state. Age plays a role as well, as older individuals tend to be more **sedentary** and are more prone to venous stasis.

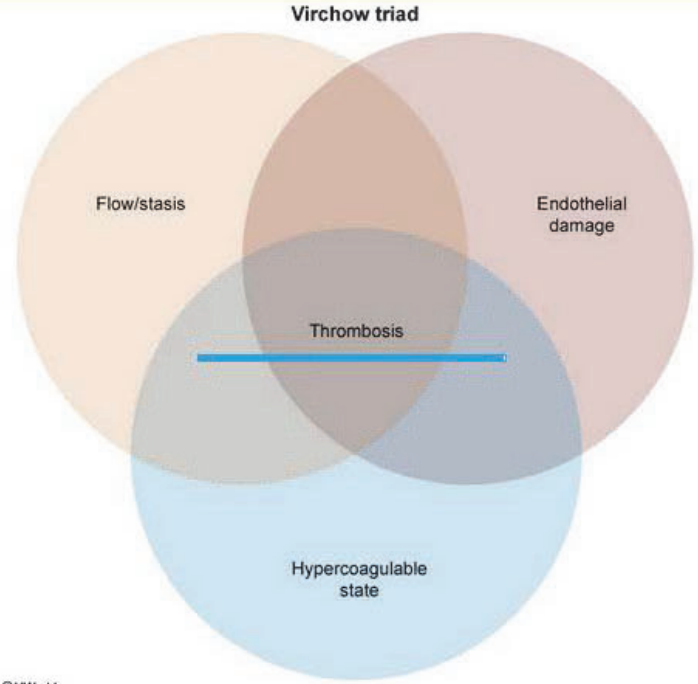
(Choice A) Atherosclerosis primarily affects the higher pressure arteries in the systemic circulation (eg, aorta, popliteal arteries, carotid arteries) and the coronary arteries. Significant atherosclerosis in the relatively low-pressure pulmonary arteries is rare.

(Choice B) Fluid overload causes pulmonary edema, typically appearing as alveolar ground glass opacities on CT scan. This patient's lungs appear clear of airspace disease.

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opacities on CT scan. This patient's lungs appear clear of airspace disease.

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(Choice A) Atherosclerosis primarily affects the higher pressure arteries in the systemic circulation (eg, aorta, popliteal arteries, carotid arteries) and the coronary arteries. Significant atherosclerosis in the relatively low-pressure pulmonary arteries is rare.

(Choice B) Fluid overload causes pulmonary edema, typically appearing as alveolar ground glass opacities on CT scan. This patient's lungs appear clear of airspace disease.

(Choice D) An intimal tear can lead to aortic dissection, which classically manifests as severe chest pain radiating to the back. Pulmonary artery dissection is extremely rare.

(Choice E) Pulmonary vasculitis (eg, granulomatosis with polyangiitis) could cause dyspnea and chest tightness but would demonstrate an interstitial pattern on CT scan, sometimes leading to pulmonary hemorrhage.

(Choice F) Rupture of pulmonary blebs (thin-walled, air-filled subpleural structures) leads to pneumothorax.

(Choice G) For pulmonary metastasis to cause significant dyspnea, multiple lesions would likely be present. There is no evidence of lung masses on this patient's CT scan.

Educational objective:

Saddle pulmonary embolism straddles the bifurcation of the main pulmonary artery. Venous

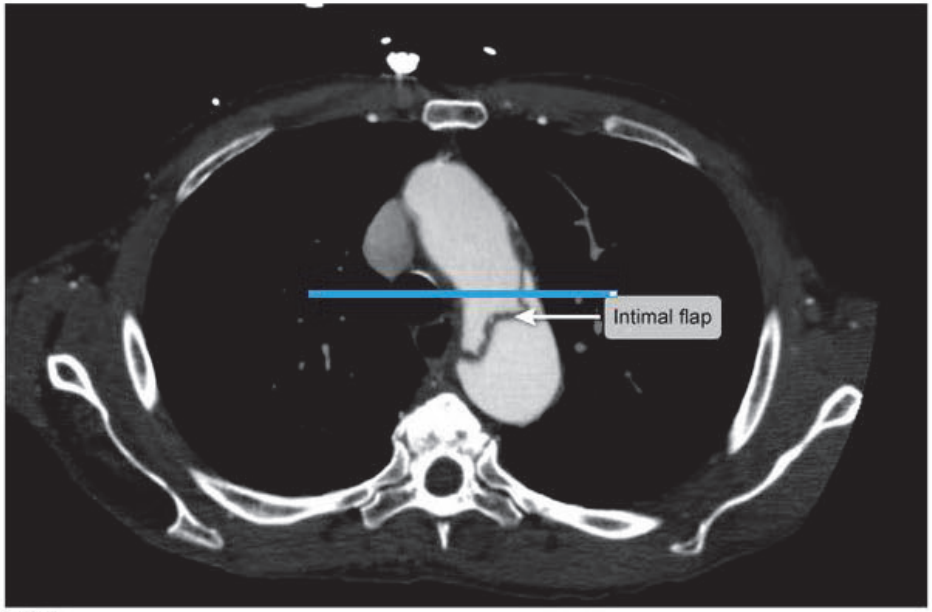
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(Choice A) Atherosclerosis primarily affects the higher pressure arteries in the systemic circulation (eg,

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Aortic dissection



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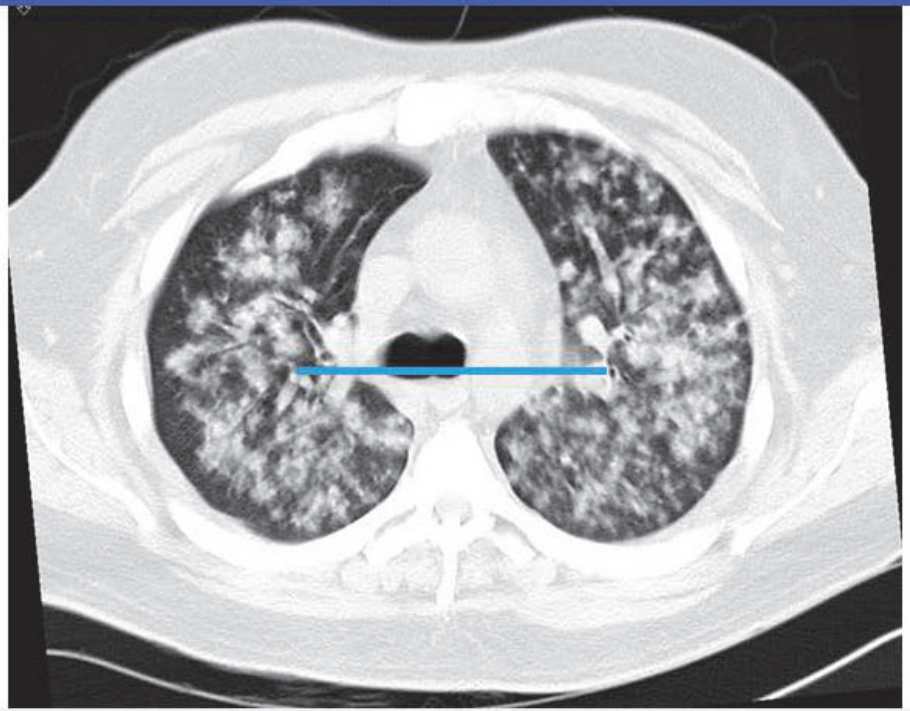
Saddle pulmonary embolism straddles the bifurcation of the main pulmonary artery. Venous

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(Choice A) Atherosclerosis primarily affects the higher pressure arteries in the systemic circulation (eg,

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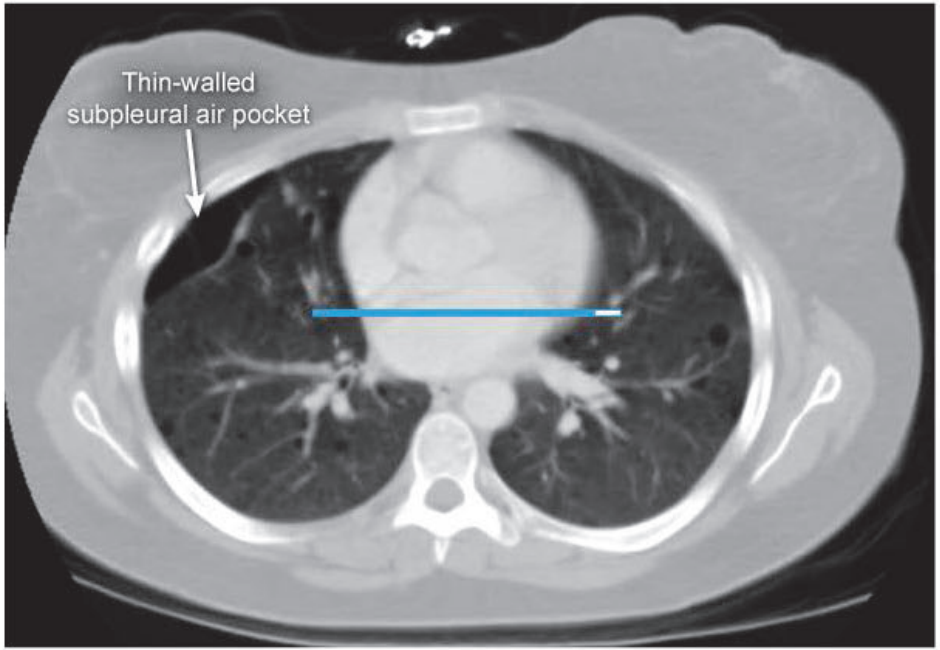
Saddle pulmonary embolism straddles the bifurcation of the main pulmonary artery. Venous

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(Choice A) Atherosclerosis primarily affects the higher pressure arteries in the systemic circulation (eg,

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Pulmonary bleb



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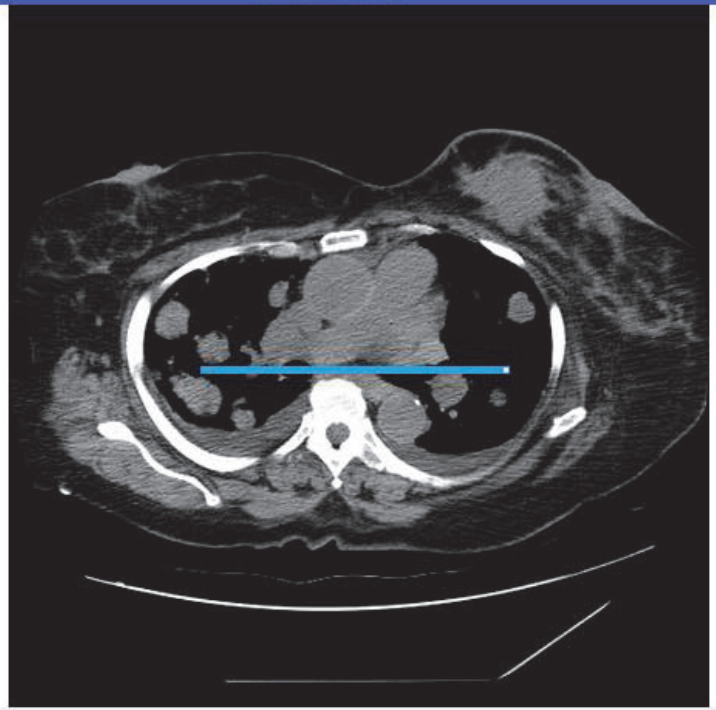
Saddle pulmonary embolism straddles the bifurcation of the main pulmonary artery. Venous

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(Choice A) Atherosclerosis primarily affects the higher pressure arteries in the systemic circulation (eg,

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Saddle pulmonary embolism straddles the bifurcation of the main pulmonary artery. Venous

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tightness but would demonstrate an interstitial pattern on CT scan, sometimes leading to pulmonary hemorrhage.

(Choice F) Rupture of pulmonary blebs (thin-walled, air-filled subpleural structures) leads to pneumothorax.

(Choice G) For pulmonary metastasis to cause significant dyspnea, multiple lesions would likely be present. There is no evidence of lung masses on this patient's CT scan.

Educational objective:

Saddle pulmonary embolism straddles the bifurcation of the main pulmonary artery. Venous thromboembolism (ie, pulmonary embolism or deep vein thrombosis) arises due to the Virchow triad of endothelial injury, venous stasis, and a hypercoagulable state. Malignancy causes a hypercoagulable state and is a strong risk factor for venous thromboembolism.

References

- Saddle pulmonary embolism diagnosed by CT angiography: frequency, clinical features and outcome.
- Saddle pulmonary embolism: is it as bad as it looks? A community hospital experience.

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www.ncbi.nlm.nih.gov/pubmed/17254761

A 56-year-old, previously healthy man has worsening fatigue and recurrent epistaxis. Evaluation shows anemia, thrombocytopenia, and abnormal circulating leukocytes. Bone marrow biopsy establishes a diagnosis of acute myeloid leukemia. The patient is initially treated with induction chemotherapy, and an allogeneic hematopoietic stem cell transplant is recommended. A nonrelated, HLA–matched donor is not found, so the patient's adult son volunteers to be the donor. The plan is for the patient to receive conditioning chemotherapy and radiotherapy followed by bone marrow transplant. Prior to transplant, a procedure is performed to deplete $CD3^+$ cells in the marrow graft. This pretransplant procedure would be most helpful in decreasing this patient's risk for which of the following?

A. Cytomegalovirus infection (2%)
✓ B. Graft versus host disease (85%)
C. ~~Immunoglobulin deficiency~~ (0%)
D. ~~Leukemia relapse~~ (7%)
E. ~~Lymphoproliferative disease~~ (4%)

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Explanation

Graft versus host disease	
Etiology	• Most commonly occurs after allogeneic hematopoietic cell transplant • Donor $CD3^+$ T cells recognize host cells as foreign → widespread, multisystem inflammatory response • Increased risk with: ◦ HLA mismatch ◦ Lack of pretransplant $CD3^+$ T-cell depletion
Clinical manifestations	• Skin: maculopapular rash, which can progress to bullous lesions • Liver: abnormal function tests (eg, increased bilirubin & alkaline phosphatase) • Gastrointestinal tract: diarrhea, abdominal pain, nausea & vomiting

HLA = human leukocyte antigen.

Allogeneic stem cell transplantation is used in the treatment of leukemia to provide a new source of hematopoietic stem cells (HSCs) after destruction of the patient's immune cells (including malignant

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Allogeneic stem cell transplantation is used in the treatment of leukemia to provide a new source of hematopoietic stem cells (HSCs) after destruction of the patient's immune cells (including malignant cells) with chemoradiotherapy. The donor's HSCs are frequently obtained from bone marrow or peripheral blood and contain differentiated immune cells such as **$CD3^+$ T cells**.

These donor $CD3^+$ ($CD4^+$/$CD8^+$) T cells can recognize human leukocyte antigen (HLA)–mismatched host cells (including residual leukemia cells) as foreign, providing a beneficial **graft versus leukemia/tumor** effect. However, they can also attack normal host cells and initiate **graft versus host disease** (GVHD), a widespread inflammatory response that characteristically damages the skin (eg, maculopapular rash), gastrointestinal tract (eg, diarrhea, abdominal pain), and liver (eg, elevated serum bilirubin).

Depletion of donor $CD3^+$ T cells prior to HSC transplant is performed primarily to **decrease GVHD risk**, but it also has the following undesirable effects on the host:

- Decreased graft versus leukemia effect, increasing the risk of leukemia relapse **(Choice D)**.
- Depletion of memory T cells, which increases the risk of viral (eg, cytomegalovirus, human herpes virus 6) infections **(Choice A)**. This also increases the risk of posttransplant lymphoproliferative disease due to the reduction in donor T cells that normally attack proliferating B cells infected with

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- Depletion of memory T cells, which increases the risk of viral (eg, cytomegalovirus, human herpes virus 6) infections **(Choice A)**. This also increases the risk of posttransplant lymphoproliferative disease due to the reduction in donor T cells that normally attack proliferating B cells infected with Epstein-Barr virus **(Choice E)**.

(Choice C) Immunoglobulin deficiency is a normal effect of myeloablative chemoradiotherapy that improves over time with engraftment (proliferation and differentiation) of donor HSCs. Removal of donor T cells before the transplant would increase the period of B cell and immunoglobulin deficiency by slowing engraftment and reestablishment of host immune function.

Educational objective:

Allogeneic hematopoietic stem cell grafts normally include donor $CD3^+$ T cells that can initiate graft versus host disease (GVHD), a widespread inflammatory response that can damage multiple organs. Depletion of donor $CD3^+$ T cells prior to transplant decreases the risk of GVHD but also decreases the beneficial graft versus tumor effect, increasing the likelihood of cancer relapse.

Pathophysiology	Hematology & Oncology	Bone marrow transplantation
Subject	System	Topic

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A researcher is studying the role of glucose metabolites in normal cellular function. A specific human cell type is incubated in glucose-rich media. Intracellular levels of glucose metabolizing enzymes, intermediate products, and generated ATP are measured. In these cells, glycolysis of a single glucose molecule always yields pyruvate but sometimes generates no net ATP. Which of the following cells is most likely being studied in this experiment?

A. Adipocytes (8%)
✓ B. Erythrocytes (70%)
C. Hepatocytes (8%)
D. Neurons (2%)
E. Skeletal muscle cells (9%)

Correct

70%
Answered correctly

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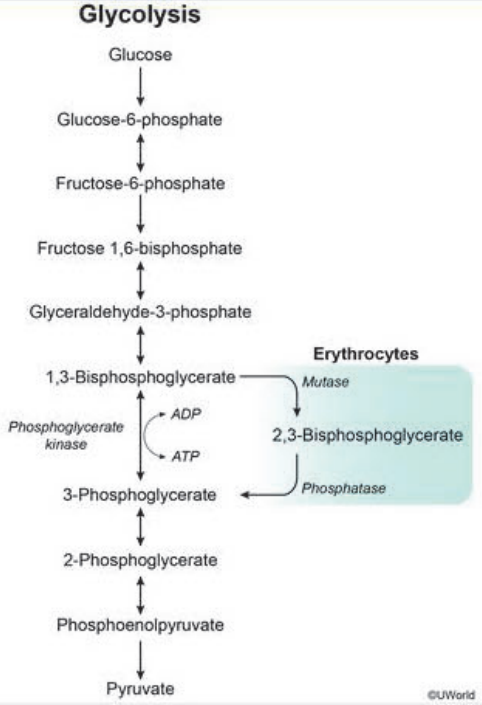
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Pyruvate

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Erythrocytes use glycolysis as the major pathway to generate energy as they do not have mitochondria and therefore cannot use the citric acid cycle. During normal glycolysis, ATP is generated when 1,3-BPG is converted to 3-phosphoglycerate by the enzyme phosphoglycerate kinase. However, erythrocytes can bypass this part of the pathway using **bisphosphoglycerate mutase**, an enzyme that converts 1,3-BPG to **2,3-BPG** in a step that produces **no ATP**. 2,3-BPG is subsequently catabolized to 3-phosphoglycerate by bisphosphoglycerate phosphatase in a step that also yields no ATP. By generating 2,3-BPG rather than proceeding with regular glycolysis, erythrocytes sacrifice the net ATP gain achieved in normal glycolysis.

The major function of erythrocytes is to carry hemoglobin-bound oxygen from the lungs to the peripheral tissues, and 2,3-BPG is a very important regulator of oxygen-hemoglobin binding. The conversion of 1,3-BPG to 2,3-BPG is increased in **hypoxia** and chronic anemia. 2,3-BPG allosterically decreases hemoglobin's affinity for oxygen. As a result, in the presence of lower blood oxygen concentrations, higher 2,3-BPG levels within erythrocytes enable **increased oxygen delivery** in the peripheral tissues.

(Choices A, C, D, and E) The enzyme bisphosphoglycerate mutase is present in large amounts in erythrocytes. However, it is present in insignificant quantities in adipocytes, hepatocytes, neurons, and myocytes; this causes virtually negligible 2,3-BPG production in these cell types.

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2,3-BPG levels within erythrocytes enable **increased oxygen delivery** in the peripheral tissues.

(Choices A, C, D, and E) The enzyme bisphosphoglycerate mutase is present in large amounts in erythrocytes. However, it is present in insignificant quantities in adipocytes, hepatocytes, neurons, and myocytes; this causes virtually negligible 2,3-BPG production in these cell types.

Educational objective:

2,3-BPG decreases hemoglobin's affinity for oxygen. Therefore, in the presence of lower blood oxygen concentrations, higher 2,3-BPG levels within erythrocytes enable increased oxygen delivery in the peripheral tissues. 2,3-BPG is produced from 1,3-BPG by the enzyme bisphosphoglycerate mutase. This reaction bypasses an ATP-generating step of glycolysis, causing no net gain in ATP.

References

- Dephosphorylation of 2,3-bisphosphoglycerate by MIPP expands the regulatory capacity of the Rapoport-Luebering glycolytic shunt.
- The energy-less red blood cell is lost: erythrocyte enzyme abnormalities of glycolysis.

Biochemistry	Hematology & Oncology	Glycolysis
Subject	System	Topic

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A 44-year-old male is hospitalized with unstable angina. On the fourth day of hospitalization he develops severe foot pain and right toe paleness. His laboratory testing is significant for platelet count of 60,000/mm^3. Treatment with argatroban is initiated immediately. The drug (argatroban) used to treat this patient's current condition has which mechanism of action?

- A. Binds to the thrombin active site (50%)
- B. Blocks glutamate residue carboxylation (4%)
- C. Block ADP receptors (15%)
- D. Block GP IIb/IIIa surface receptors (22%)
- E. Inhibits phosphodiesterase (6%)

Correct

50%
Answered correctly

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Last Updated

Explanation

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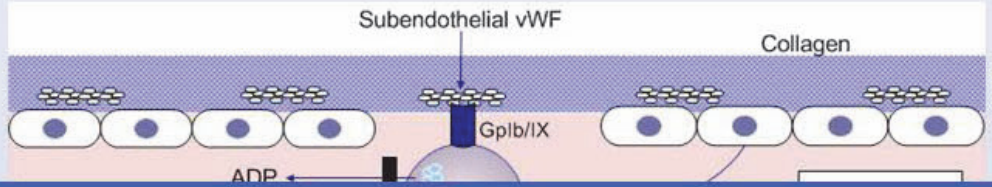
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Heparin is the most important cause of thrombocytopenia in hospitalized patients. Occurrence of heparin-induced thrombocytopenia (HIT) is much more common with the use of unfractionated heparin compared to low molecular weight heparin. HIT more commonly leads to paradoxical thrombosis rather than bleeding. HIT is a serious disorder caused by antibodies to heparin and platelet factor IV.

Direct thrombin inhibitors (hirudin, lepirudin and argatroban) do not require antithrombin-III for their action and are drugs of choice in the treatment of HIT. Patients with HIT need ongoing anticoagulation due to the presence of, or possibility of thrombosis. Upon clinical suspicion of HIT, the most important initial step in treatment is to stop all forms of heparin.

(Choice B) Warfarin inhibits vitamin K dependent γ-carboxylation of glutamic acid residues of clotting factors II, VII, IX and X.

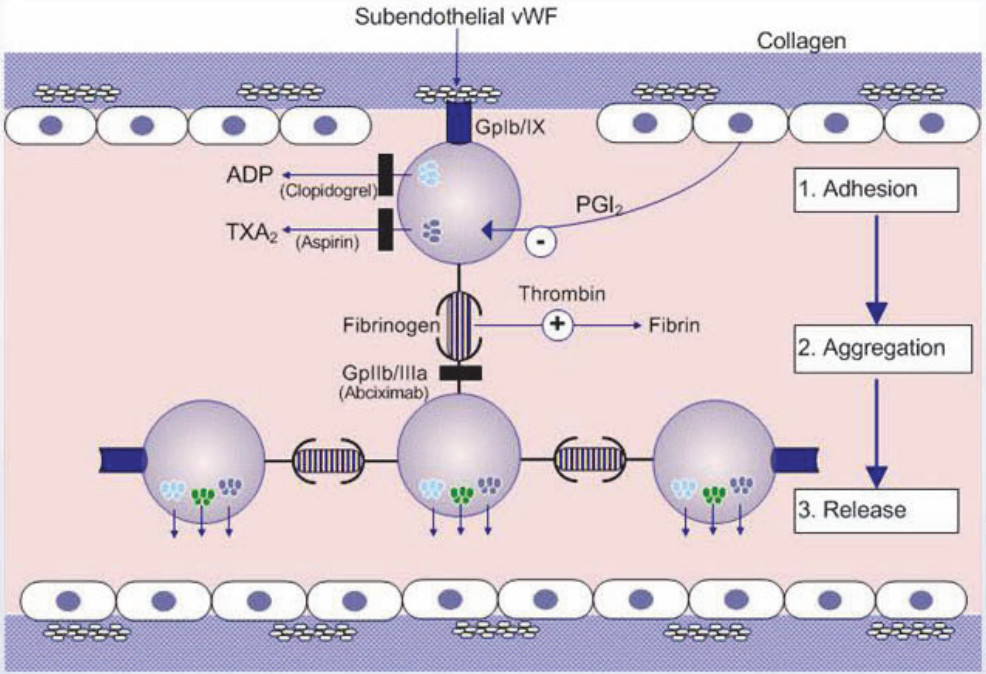
(Choices C, D and E) Platelet plug formation involves three critical steps: adhesion, aggregation and release (see diagram). Drugs that inhibit platelet aggregation work by different mechanisms.



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release (see diagram). Drugs that inhibit platelet aggregation work by different mechanisms.



Aspirin irreversibly acetylates platelet cyclooxygenase-I leading to decreased formation of thromboxane A2.

Aspirin is used for primary and secondary prevention of myocardial infarction and strokes.

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Aspirin irreversibly acetylates platelet cyclooxygenase-I leading to decreased formation of thromboxane A2. Aspirin is used for primary and secondary prevention of myocardial infarction and strokes.

Ticlopidine and clopidogrel inhibit ADP mediated platelet aggregation. They are useful following percutaneous coronary intervention (PCI), and for treatment of unstable angina and non-Q wave myocardial infarction.

Dipyridamole and cilostazol inhibit platelet aggregation by inhibiting phosphodiesterase activity and increasing cAMP.

Glycoprotein IIb/IIIa inhibitors inhibit binding of platelet glycoprotein IIb/IIIa with fibrinogen and fibronectin. The glycoprotein IIb/IIIa inhibitors abciximab, eptifibatide and tirofiban are approved for use following percutaneous intervention (PCI) in acute coronary syndrome.

Educational objective:
Heparin-induced thrombocytopenia (HIT) is treated with direct thrombin inhibitors (DTIs) such as argatroban. Both high molecular weight heparin and LMWH should be avoided in these patients.

Pharmacology Hematology & Oncology Anticoagulants

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A 63-year-old man comes to the hospital due to sudden onset chest pain and dyspnea. He has a history of glioblastoma multiforme, for which he has been undergoing radiation treatment. His temperature is 36.1 C (97 F), blood pressure is 110/80 mm Hg, pulse is 118/min, and respirations are 26/min. Pulse oximetry shows 90% on room air. A CT pulmonary angiogram demonstrates a left-sided pulmonary embolism. The patient is started on continuous unfractionated heparin infusion. Several hours later, the patient begins to experience severe headache and quickly becomes unconscious. A CT of the head reveals bleeding into the tumor. After stopping the heparin infusion, administration of which of the following is indicated for immediate anticoagulant reversal?

A. Fresh frozen plasma (14%)
B. Platelets (1%)
C. Protamine (78%)
D. Prothrombin complex concentrate (3%)
E. Tranexamic acid (1%)
F. Vitamin K (1%)

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Explanation

	Warfarin overdose	Heparin overdose
Vitamin K	• Effective (takes days)	• Ineffective
FFP	• Effective (contains all blood clotting factors & proteins)	• Ineffective (contains antithrombin III → enhances heparin effect)
Protamine	• Ineffective	• Effective (heparin-specific antidote)

FFP = fresh frozen plasma.

Unfractionated heparin (UFH) and low-molecular weight heparins (LMWHs) are commonly used anticoagulants in the hospital setting. Heparin increases the effect of the naturally occurring anticoagulant antithrombin III (ATIII). Activated partial thromboplastin time (aPTT) is measured to monitor the therapeutic effect of heparin. Bleeding and heparin-induced thrombocytopenia are serious complications of heparin therapy. **Bleeding** due to heparin toxicity is treated with **protamine** sulfate, a specific antagonist. Protamine sulfate is a peptide that binds to heparin, forming a complex that has no anticoagulant activity

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FFP = fresh frozen plasma.

Unfractionated heparin (UFH) and low-molecular weight heparins (LMWHs) are commonly used anticoagulants in the hospital setting. Heparin increases the effect of the naturally occurring anticoagulant antithrombin III (ATIII). Activated partial thromboplastin time (aPTT) is measured to monitor the therapeutic effect of heparin. Bleeding and heparin-induced thrombocytopenia are serious complications of heparin therapy. **Bleeding** due to heparin toxicity is treated with **protamine** sulfate, a specific antagonist. Protamine sulfate is a peptide that binds to heparin, forming a complex that has no anticoagulant activity. Although protamine is often used in the management of LMWH toxicity, it does not completely reverse the anti-Xa activity of LMWH.

Vitamin K is used for reversal of **warfarin** overdose but requires new synthesis of coagulation factors. As a result, its full effect takes time to manifest. For this reason, in the setting of acute life-threatening bleeding due to warfarin, fresh frozen plasma (**FFP**) (contains all blood proteins and clotting factors) should be given. However, FFP is **not** useful for heparin overdose as it contains ATIII, which can further potentiate the effects of heparin. **Prothrombin complex concentrates** (PCCs), which contain the vitamin K-dependent factors II, VII, IX, and X, can be used to treat bleeding due to warfarin (not heparin) overdose **(Choices A, D, and F)**.

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Vitamin K is used for reversal of **warfarin** overdose but requires new synthesis of coagulation factors. As a result, its full effect takes time to manifest. For this reason, in the setting of acute life-threatening bleeding due to warfarin, fresh frozen plasma (**FFP**) (contains all blood proteins and clotting factors) should be given. However, FFP is **not** useful for heparin overdose as it contains ATIII, which can further potentiate the effects of heparin. **Prothrombin complex concentrates** (PCCs), which contain the vitamin K-dependent factors II, VII, IX, and X, can be used to treat bleeding due to warfarin (not heparin) overdose **(Choices A, D, and F)**.

(Choices B and E) Platelet function is not affected by warfarin therapy. Aminocaproic acid and tranexamic acid inhibit fibrinolysis by inhibiting plasminogen activation.

Educational objective:
Protamine sulfate binds to heparin, causing chemical inactivation. Vitamin K and fresh frozen plasma can be used to reverse warfarin effects.

Pharmacology	Hematology & Oncology	Anticoagulants
Subject	System	Topic

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A 61-year-old man comes to the hospital due to 2 days of right leg swelling. He recently flew back to the United States from Japan, where he was visiting his daughter who is spending a semester abroad. The patient has a medical history of hypertension and hyperlipidemia. Temperature is 37.2 C (99 F), blood pressure is 136/70 mm Hg, and pulse is 90/min. Pulse oximetry shows 99% on room air. Cardiopulmonary examination is within normal limits. There is tenderness and swelling of the right lower extremity up to the mid thigh. Laboratory studies, including prothrombin time and activated partial thromboplastin time, are normal. Venous doppler reveals an occluding thrombus in the right femoral and popliteal veins. The patient is started on rivaroxaban. This drug inhibits which of the following?

- A. Factor VIII (0%)
- ✓ B. Factor Xa (87%)
- C. Glycoprotein IIb/IIIa (3%)
- D. Platelet P2Y12 (1%)
- E. Thrombin (6%)

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*Major mechanism of action; antithrombin III has some inhibition on all activated coagulation factors.
LMW = low molecular weight.
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This patient has right lower extremity proximal deep venous thrombosis (DVT), with his recent long flight from Japan being a possible risk factor. Many patients with DVT receive long-term anticoagulation with warfarin. Alternates include direct **factor Xa** inhibitors (eg, rivaro**Xa**ban, api**Xa**ban), which bind to the active site of factor Xa and prevent thrombin formation. These drugs can be administered orally as monotherapy and do not require laboratory monitoring. They are used for venous thromboembolism treatment as well as for stroke prophylaxis in patients with atrial fibrillation (who are at risk for embolic stroke).

(Choice A) Factor VIII replacement (not inhibition) is the mainstay of hemophilia A treatment.

(Choice C) Eptifibatide inhibits platelet aggregation and thrombosis by blocking the glycoprotein IIb/IIIa receptor, which is the binding site for fibrinogen. This drug is typically used in acute coronary syndrome and in patients undergoing percutaneous coronary intervention.

(Choice D) Ticagrelor binds the adenosine diphosphate (ADP) P2Y12 receptor on platelets, which prevents platelet aggregation by blocking ADP-mediated activation of the glycoprotein IIb/IIIa receptor complex. This drug is also used in acute coronary syndrome and in patients undergoing percutaneous coronary intervention.

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and in patients undergoing percutaneous coronary intervention.

(Choice D) Ticagrelor binds the adenosine diphosphate (ADP) P2Y12 receptor on platelets, which prevents platelet aggregation by blocking ADP-mediated activation of the glycoprotein IIb/IIIa receptor complex. This drug is also used in acute coronary syndrome and in patients undergoing percutaneous coronary intervention.

(Choice E) Dabigatran is an oral direct thrombin inhibitor that inactivates both circulating and clot-associated thrombin. It is also used for treatment of thromboembolic disease and stroke prophylaxis in atrial fibrillation.

Educational objective:

Rivaroxaban is an oral anticoagulant that directly inhibits factor Xa. It is used in venous thromboembolism and atrial fibrillation.

References

- New oral anticoagulants: their advantages and disadvantages compared with vitamin K antagonists in the prevention and treatment of patients with thromboembolic events.

Pharmacology	Hematology & Oncology	Venous thromboembolism
Subject	System	Topic

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and in patients undergoing percutaneous coronary intervention.

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Educational objective:

Rivaroxaban is an oral anticoagulant that directly inhibits factor Xa. It is used in venous thromboembolism and atrial fibrillation.

References

- New oral anticoagulants: their advantages and disadvantages compared with vitamin K antagonists in the prevention and treatment of patients with thromboembolic events.

Pharmacology	Hematology & Oncology	Venous thromboembolism
Subject	System	Topic

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A 34-year-old man comes to the emergency department due to a facial injury. He reports getting hit on the face during a fistfight at a bar. Examination shows dark blue periorbital ecchymosis on the right side. Ophthalmic and neurologic examinations are otherwise normal. After appropriate evaluation, the patient is discharged home. Several days later, the bruise becomes greenish in color. This change in color is best explained by the activity of which of the following enzymes?

A. Bilirubin glucuronyl transferase (17%)
B. Ferrochelatase (8%)
✓ C. Heme oxygenase (54%)
D. Porphobilinogen deaminase (12%)
E. Uroporphyrinogen decarboxylase (6%)

Correct

54%
Answered correctly

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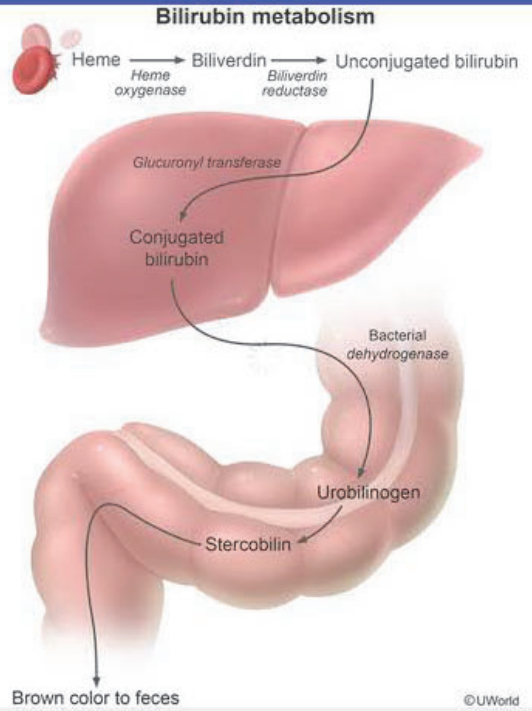
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Exhibit Display



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This patient has a resolving **hematoma** after a traumatic injury. Following the injury, hemoglobin-containing erythrocytes escape into the periorbital tissues, giving the bruise its initial purple or bluish color. Erythrocyte destruction causes the release of iron-containing heme molecules. **Heme oxygenase** (contained in macrophages, among other cells) degrades heme into **biliverdin**, carbon monoxide, and ferrous iron while consuming oxygen and electrons provided by NADH and NADPH-cytochrome P450 reductase. Biliverdin is **green** in color and is further reduced (by the enzyme biliverdin reductase) to the yellow pigment bilirubin, which is then transported to the liver bound to albumin.

(Choice A) Bilirubin glucuronyl transferase, or uridine 5'-diphospho-glucuronyl transferase (UGT), is the enzyme necessary for bilirubin conjugation to glucuronic acid. Lack of UGT or the use of medications that interfere with its activity impairs the liver's ability to conjugate bilirubin.

(Choices B, D, and E) Ferrochelatase (inhibited by lead) is the final enzyme in the heme synthetic pathway. Porphobilinogen deaminase (PBG deaminase) and uroporphyrinogen decarboxylase (UROD) are also involved in heme production, not degradation; UROD deficiency can be seen in porphyria cutanea tarda, the most common porphyria, and PBG deaminase deficiency can be seen in acute intermittent porphyria.

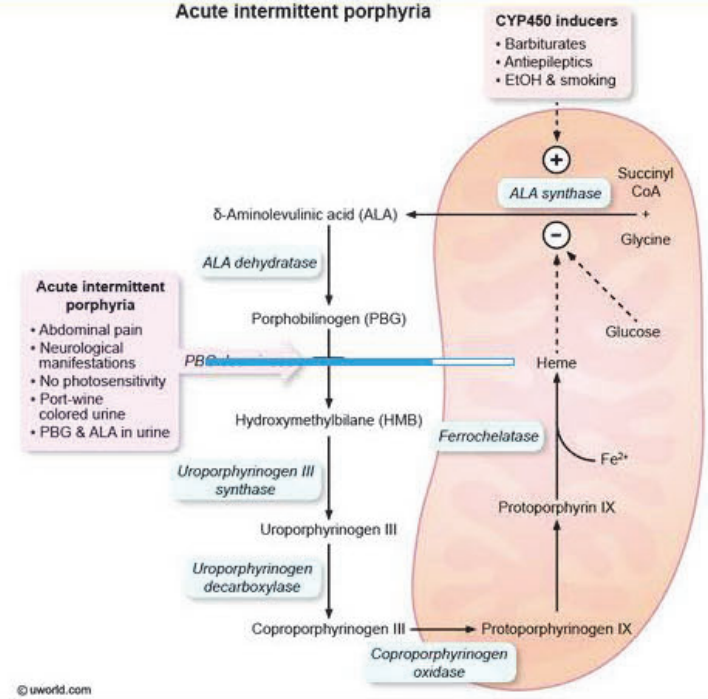
Educational objective:

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Exhibit Display



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Educational objective:

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Educational objective:
Heme oxygenase converts heme to biliverdin, a pigment that causes the greenish color to develop in bruises several days after an injury.

Biochemistry	Hematology & Oncology	Heme metabolism
Subject	System	Topic

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A 36-year-old woman with mitral valve prolapse comes to the office due to dyspnea and is found to have severe mitral valve regurgitation. Two weeks later, the patient undergoes elective mechanical mitral valve replacement. Continuous heparin infusion and oral warfarin are initiated following the procedure. Coagulation studies during admission are as follows:

Postoperative day	1	2	3	4
INR	1.1	1.5	1.8	2.1
PTT(seconds)	72	76	74	78

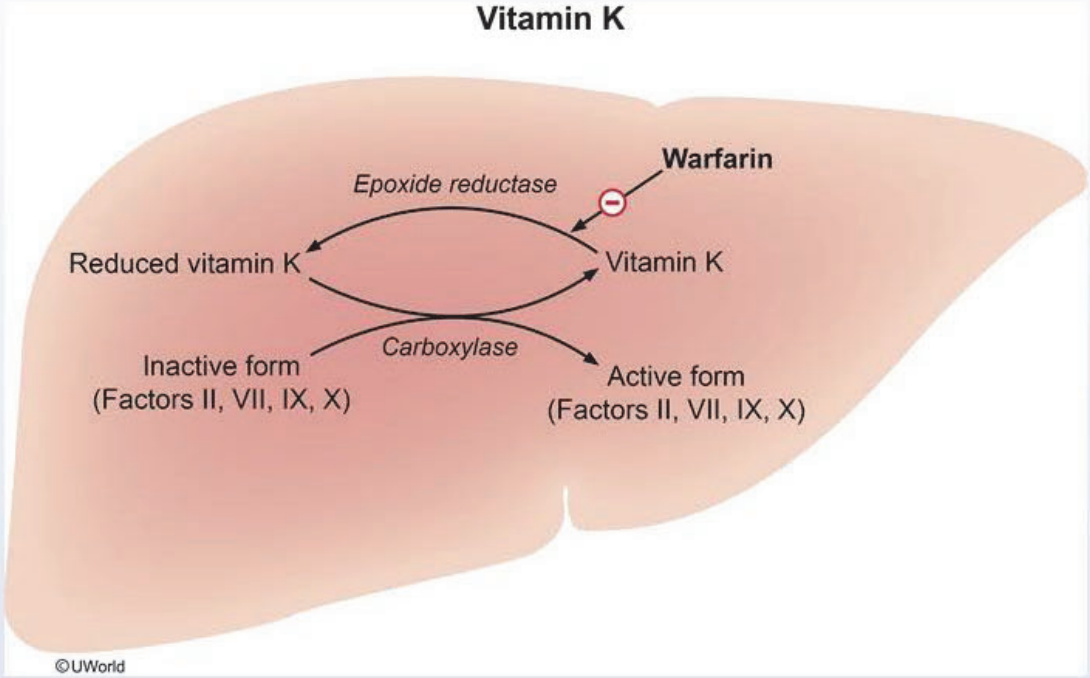
The patient achieves the goal of INR ≥2.5 on postoperative day 5 and heparin infusion is discontinued. Which of the following likely caused the delay in achieving therapeutic INR in this patient?

- A. Clotting factors generated before warfarin initiation (58%)
- B. Formation of anti-platelet factor 4/heparin antibodies (4%)
- C. High total body stores of vitamin K (9%)

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Explanation



Warfarin is a vitamin K antagonist that blocks **epoxide reductase** in the liver, leading to impaired vitamin K recycling. This depletes the reduced form of vitamin K, which is required for gamma carboxylation of

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Warfarin is a vitamin K antagonist that blocks **epoxide reductase** in the liver, leading to impaired vitamin K recycling. This depletes the reduced form of vitamin K, which is required for gamma carboxylation of **vitamin K–dependent clotting factors** (II, VII, IX, and X). In the absence of gamma carboxylation, vitamin K–dependent clotting factors cannot bind calcium or phospholipid membranes to induce coagulation.

Because warfarin inhibits gamma carboxylation of **new** vitamin K–dependent clotting factors, therapeutic efficacy is delayed until **preexisting clotting factors** in the plasma are consumed. Although INR tends to slowly increase in the first few days of administration due to the short half-life of factor VII (4-6 hours), full **therapeutic effect** does not typically occur for **3 days** due to the long half-life of **factor II**.

Warfarin also inhibits gamma carboxylation of the proteins C and S. Because these proteins exert an anticoagulant effect, the initiation of warfarin can be associated with an initial procoagulant state. However, once preexisting vitamin K–dependent clotting factors are consumed, an anticoagulant effect is established.

(Choice B) Anti-platelet factor 4/heparin antibodies cause heparin-induced thrombocytopenia, which typically arise 5-10 days after heparin initiation. This condition is marked by thrombocytopenia and a high risk of arterial and venous thrombosis, but would not result in a delay in therapeutic INR following warfarin

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risk of arterial and venous thrombosis, but would not result in a delay in therapeutic INR following warfarin administration.

(Choice C) Total body vitamin K is sufficient for several weeks; it does not contribute to a delay in warfarin efficacy. However, increased intake of foods rich in vitamin K (eg, green leafy vegetables) can lead to subtherapeutic INR due to increased vitamin K availability in the liver.

(Choice D) Warfarin is metabolized by the hepatic cytochrome P450 2C9 enzyme. Because many other medications induce or inhibit this enzyme, warfarin is susceptible to a wide range of drug interactions. However, the delay in achieving therapeutic INR is primarily due to the presence of preexisting clotting factors.

(Choice E) Warfarin reaches maximal plasma concentration approximately 90 minutes after administration. The delay in efficacy is due to the presence of preexisting clotting factors.

Educational objective:
Warfarin blocks epoxide reductase, which lowers the reduced form of vitamin K in the liver; this prevents gamma carboxylation of vitamin K–dependent clotting factors (II, VII, IX, and X). Because warfarin only blocks the generation of new clotting factors, therapeutic effect is delayed 3-5 days until preexisting clotting factors are consumed.

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A 32-year-old Caucasian woman experiences three episodes of deep venous thrombosis in a six year period. She has a history of pulmonary embolism as well. The patient's partial thromboplastin time (PTT) is within normal limits, and remains unchanged when activated protein C is added to her plasma. The most likely cause of this patient's problem is:

A. Immune (18%)
B. Nutritional (4%)
C. Inherited (70%)
D. Infectious (1%)
E. Neoplastic (5%)

Correct

70%
Answered correctly

30 secs
Time Spent

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Last Updated

Explanation

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This is a young patient with recurrent deep venous thromboses, features indicative of a hypercoagulable state. Inherited causes of hypercoagulability must be considered in all patients under age 50 who present with thromboses in the absence of any obvious explanation for an acquired prothrombotic state.

The patient's plasma is resistant to the normally antithrombotic effects of activated protein C. Thus, the most likely diagnosis is a mutation in the factor V gene, which renders factor Va resistant to inactivation by activated protein C. Approximately 2–15% of Caucasians carry a specific factor V mutation, the Leiden mutation. The factor V Leiden mutation and mutations in the prothrombin gene are the most common inherited causes of hypercoagulability. Activated protein C resistance (factor V Leiden mutation) is detected in approximately 20% (range 12–40%) of patients with abnormal venous thromboses.

(Choice A) Antiphospholipid antibody syndrome is a common immune cause of hypercoagulability. This condition is defined by the presence of antiphospholipid antibodies (lupus anticoagulant and/or anticardiolipin antibodies) plus one or more of the following: venous thromboembolism, arterial thromboembolism, or frequent fetal loss. Unlike the patient in the vignette, patients with antiphospholipid antibody syndrome typically have a prolonged baseline aPTT. Lupus anticoagulants are the most common cause of aPTT prolongation.

(Choice B) Folic acid deficiency can cause hyperhomocysteinemia, which is a prothrombotic state.

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However, activated protein C resistance is not seen with this condition.

(Choice D) Endovascular infections and/or systemic inflammatory states may affect vascular endothelial cells in a way that favors thrombosis. However, infection and inflammatory mediators do not directly promote activated protein C resistance in the aPTT coagulation test.

(Choice E) A paraneoplastic syndrome of hypercoagulability may be seen in some patients with cancer, especially patients with adenocarcinomas of the pancreas, colon, or lung. The mechanism of cancer-induced hypercoagulability is thought to involve release of procoagulant tumor products. Vascular stasis due to obstruction of blood flow by the tumor, patient immobility, hepatic involvement and dysfunction, sepsis, and advanced age may also contribute to the tendency toward thrombosis in cancer patients. None of these mechanisms/factors directly promotes activated protein C resistance in the aPTT coagulation test.

Educational Objective:
Inherited causes of hypercoagulability should be considered in patients younger than age 50 who present with thrombosis and no obvious explanation for an acquired prothrombotic state. The factor V Leiden mutation, which causes factor Va resistance to inactivation by activated protein C, may account for approximately 20% of cases of atypical venous thrombosis.

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A 64-year-old woman is hospitalized for elective hip replacement surgery. She has osteoarthritis and is experiencing progressive right hip pain that limits her daily activities. The patient also has a history of hypertension and hypothyroidism. Her blood pressure is 130/80 mm Hg and pulse is 90/min. BMI is 31.5 kg/m^2. Her serum creatinine is 0.9 mg/dL. She undergoes surgery without complications and is postoperatively started on a medication that is a low molecular weight fraction of a negatively charged chemical stored in mast cell granules. Which of the following is the most likely mechanism of action of the medication used?

- A. Binds antithrombin III (78%)
- B. Binds to the thrombin active site (13%)
- C. Blocks ADP receptors (3%)
- D. Combines with proactivator plasminogen (2%)
- E. Inhibits arachidonate product formation (2%)

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Nonambulatory hospitalized patients are at increased risk for developing lower extremity **deep venous thrombosis** (DVT), which can lead to pulmonary embolism. In patients undergoing elective surgery without **prophylaxis** against DVT, the risk can be even higher, particularly with certain orthopedic procedures such as hip and knee replacement. In such cases, DVT prophylaxis is usually initiated within hours of wound closure.

Unfractionated and low molecular weight **heparins** (LMWHs) are commonly used for DVT prevention in inpatient settings. Administration of heparin (a negatively charged chemical naturally present in mast cells) increases the effect of the naturally occurring anticoagulant **antithrombin III (AT III)**. Unfractionated heparin binds to AT III via a pentasaccharide in the heparin chain. This results in a conformational change of AT III, which subsequently inhibits factor Xa and neutralizes thrombin, promoting anticoagulation. AT III activated by **LMWH** (which has better bioavailability and does not need laboratory monitoring when given therapeutically) acts predominantly on **factor Xa**, not thrombin.

(Choice B) Direct thrombin inhibitors directly inhibit thrombin-mediated fibrin formation. Lepirudin and argatroban (parenteral) are primarily used for management of heparin-induced thrombocytopenia. Dabigatran (oral) is used for DVT prevention and treatment and for stroke prevention in atrial fibrillation.

(Choice C) Clopidogrel and ticlopidine inhibit ADP-mediated platelet aggregation. They are useful

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argatroban (parenteral) are primarily used for management of heparin-induced thrombocytopenia. Dabigatran (oral) is used for DVT prevention and treatment and for stroke prevention in atrial fibrillation.

(Choice C) Clopidogrel and ticlopidine inhibit ADP-mediated platelet aggregation. They are useful following percutaneous coronary intervention and for treatment of unstable angina and non-ST segment elevation myocardial infarction.

(Choice D) Use of drugs that convert inactive plasminogen to plasmin leads to fibrinolysis and clot lysis; such medications are given for clot lysis in acute myocardial infarction, pulmonary embolism, and arterial thrombosis.

(Choice E) Aspirin irreversibly acetylates platelet cyclooxygenase-I, leading to decreased formation of thromboxane A2. Aspirin is used for primary and secondary prevention of myocardial infarction and stroke.

Educational objective:
Heparin is commonly used for the prevention of deep venous thrombosis in nonambulatory patients or those undergoing elective surgery, especially hip and knee surgery. Heparin increases the effect of the naturally occurring anticoagulant antithrombin III.

References

- New Antithrombotic Drugs: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American

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(Choice C) Clopidogrel and ticlopidine inhibit ADP-mediated platelet aggregation. They are useful following percutaneous coronary intervention and for treatment of unstable angina and non-ST segment elevation myocardial infarction.

(Choice D) Use of drugs that convert inactive plasminogen to plasmin leads to fibrinolysis and clot lysis; such medications are given for clot lysis in acute myocardial infarction, pulmonary embolism, and arterial thrombosis.

(Choice E) Aspirin irreversibly acetylates platelet cyclooxygenase-I, leading to decreased formation of thromboxane A2. Aspirin is used for primary and secondary prevention of myocardial infarction and stroke.

Educational objective:
Heparin is commonly used for the prevention of deep venous thrombosis in nonambulatory patients or those undergoing elective surgery, especially hip and knee surgery. Heparin increases the effect of the naturally occurring anticoagulant antithrombin III.

References

- New Antithrombotic Drugs: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American

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www.ncbi.nlm.nih.gov/pubmed/18413611

A 63-year-old man comes to the emergency department because of 1 hour of sudden-onset chest pain. He developed the pain after eating dinner and did not have relief with antacids. His other medical problems include hypertension, hyperlipidemia, and type 2 diabetes mellitus. In the emergency department, his blood pressure is 100/60 mm Hg, pulse is 100/min, and respirations are 18/min. His EKG shows ST-segment depression in the inferior leads, and his cardiac serum troponin T is positive. The following anticoagulants are being considered for treatment:

Anticoagulant	Molecular Weight
Unfractionated heparin	5000-30,000 u
Enoxaparin	3000-8000 u
Fondaparinux	Pentasaccharide

Which of the following anticoagulants is most effective in inactivating thrombin?

A. Enoxaparin (27%)

B. Fondaparinux (18%)

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www.ncbi.nlm.nih.gov/pubmed/18413611

Unfractionated heparin	5000-30,000 u
Enoxaparin	3000-8000 u
Fondaparinux	Pentasaccharide

Which of the following anticoagulants is most effective in inactivating thrombin?

A. Enoxaparin (27%)

B. Fondaparinux (18%)

C. Unfractionated heparin (54%)

Correct

54%
Answered correctly

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Time Spent

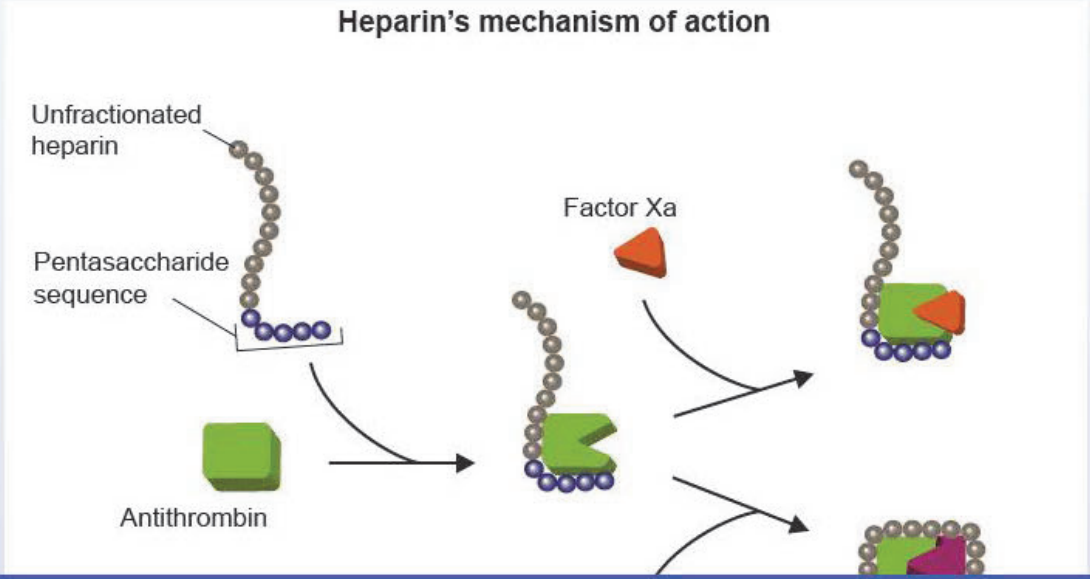
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Explanation

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www.ncbi.nlm.nih.gov/pubmed/18413611

This patient presents with findings consistent with acute coronary syndrome, with ongoing injury as evidenced by the positive troponin. An important component of therapy involves not only treating the existing clot but also preventing its propagation. The coagulation cascade amplifies the generation of thrombin, which activates platelets to form a plug and also helps convert fibrinogen to fibrin to reinforce the platelet plug. Antithrombin can inhibit both Factor Xa in the coagulation cascade and also thrombin.



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www.ncbi.nlm.nih.gov/pubmed/18413611

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Both unfractionated heparin and low molecular weight heparin (LMWH) contain a pentasaccharide sequence that binds to antithrombin and causes a conformational change that increases its ability to inactivate Factor Xa. However, heparin must bind to both antithrombin and thrombin together to form a ternary complex to inactivate thrombin. Only unfractionated heparin (not LMWH) has a pentasaccharide chain long enough (>18 saccharide units) to bind to both antithrombin and thrombin. As a result, unfractionated heparin has equal activity against Factor Xa and thrombin, while LMWH has greater activity against Factor Xa than thrombin.

(Choice A) Enoxaparin is a low molecular weight heparin that has fewer of the required long saccharide units that bind to thrombin and less antithrombotic activity compared to unfractionated heparin.

(Choice B) Fondaparinux is a synthetic pentasaccharide Factor Xa inhibitor. It has none of the required long saccharide units that bind to thrombin and much lower antithrombin activity compared to unfractionated heparin.

Educational objective:
Both unfractionated heparin and LMWH can bind to antithrombin to increase its activity against Factor Xa. Only unfractionated heparin is able to bind to both antithrombin and thrombin to allow antithrombin to

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www.ncbi.nlm.nih.gov/pubmed/18413611

(Choice A) Enoxaparin is a low molecular weight heparin that has fewer of the required long saccharide units that bind to thrombin and less antithrombotic activity compared to unfractionated heparin.

(Choice B) Fondaparinux is a synthetic pentasaccharide Factor Xa inhibitor. It has none of the required long saccharide units that bind to thrombin and much lower antithrombin activity compared to unfractionated heparin.

Educational objective:

Both unfractionated heparin and LMWH can bind to antithrombin to increase its activity against Factor Xa. Only unfractionated heparin is able to bind to both antithrombin and thrombin to allow antithrombin to inactivate thrombin.

References

- Role of ternary complexes, in which heparin binds both antithrombin and proteinase, in the acceleration of the reactions between antithrombin and thrombin or factor Xa

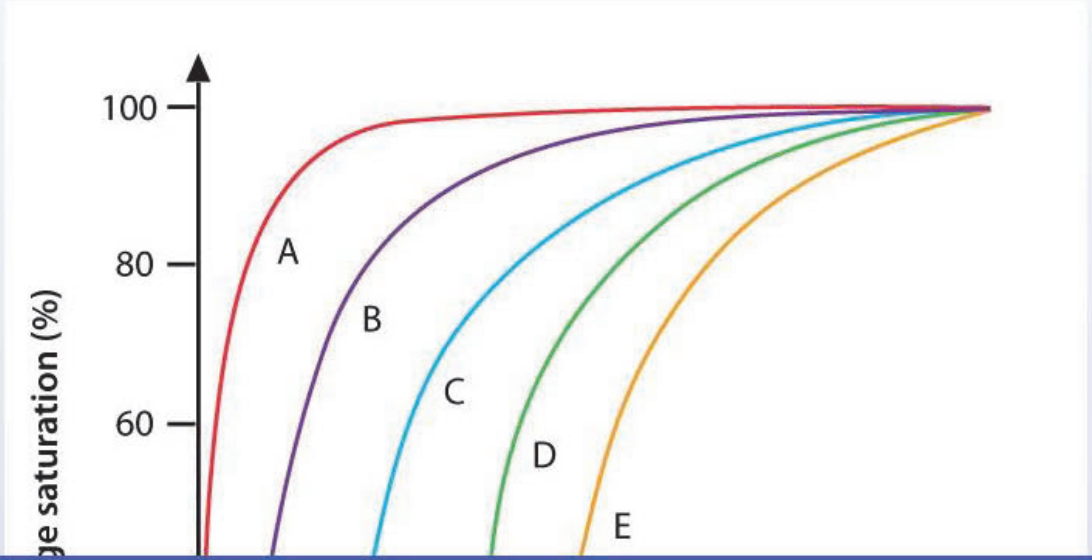
Pharmacology	Hematology & Oncology	Anticoagulants
Subject	System	Topic

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www.ncbi.nlm.nih.gov/pubmed/18413611

Scientists studying the principles behind oxygen-hemoglobin dissociation have discovered a way to successfully separate hemoglobin tetramers into individual alpha and beta subunits. During an experiment, a solution is created that contains only monomeric beta-hemoglobin subunits under physiologic conditions. If measured, the oxygen dissociation curve of the dissolved beta subunits will most likely resemble which of the following lines?

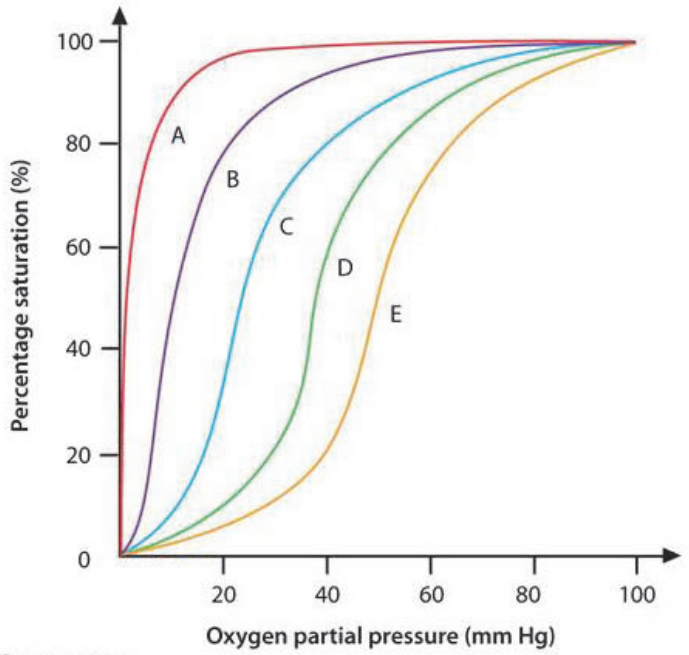


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www.ncbi.nlm.nih.gov/pubmed/18413611

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www.ncbi.nlm.nih.gov/pubmed/18413611



- A. Line A (52%)
- B. Line B (9%)
- C. Line C (8%)
- D. Line D (8%)
- E. Line E (20%)

Correct

52%
Answered correctly

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10/12/2020
Last Updated

Explanation

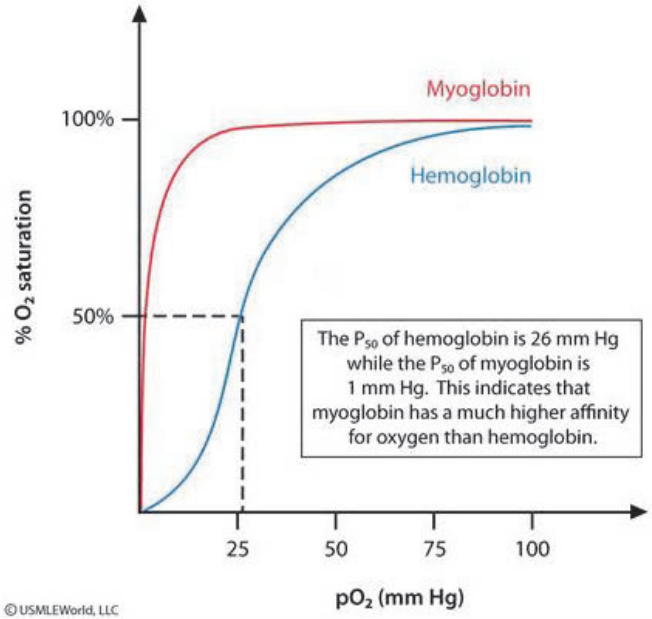
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Oxygen-dissociation curves of hemoglobin & myoglobin



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pO_2 (mm Hg)

Hemeproteins such as hemoglobin and myoglobin contain heme groups that are used to reversibly bind oxygen for transportation and storage. Hemoglobin A (the major form of hemoglobin in adults) is a tetramer consisting of 2 alpha and 2 beta chains. Each hemoglobin subunit is associated with a heme moiety, so each hemoglobin molecule has 4 heme groups. After binding to 1 oxygen molecule, the oxygen affinity of other heme molecules increases; this heme-heme interaction is responsible for the characteristic sigmoid shape of the oxygen-hemoglobin dissociation curve.

In contrast to hemoglobin, myoglobin is a monomeric protein and the primary oxygen-storing protein in skeletal and cardiac muscle tissue; it is only found in the bloodstream after muscle injury. The partial pressure of oxygen at which 50% of myoglobin molecules are oxygen saturated (P_{50}) is only 1 mm Hg, which is much lower than the P_{50} of hemoglobin (26 mm Hg). Myoglobin also has only a single heme group and so does not experience heme-heme interactions; therefore, its oxygen-dissociation curve is hyperbolic.

The secondary and tertiary structures of myoglobin and the hemoglobin beta subunit are almost identical (the α-subunits are also very similar to myoglobin). Because individual hemoglobin subunits are structurally similar to myoglobin, their oxygen-binding behavior is also similar. That is, if a hemoglobin molecule is dissociated, the individual subunits will have a hyperbolic oxygen-dissociation curve **(Choice**

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molecule is dissociated, the individual subunits will have a hyperbolic oxygen-dissociation curve **(Choice A)**.

(Choice B) Line B is left-shifted compared to normal hemoglobin A, which could indicate a high oxygen affinity hemoglobin (eg, fetal hemoglobin). Hemoglobin A will also undergo a left shift in the presence of factors such as increased pH, decreased temperature, and decreased 2,3-diphosphoglycerate.

(Choice C) Line C depicts the normal oxygen-hemoglobin dissociation curve, with the typical sigmoidal relationship of pO_2 to hemoglobin O_2 saturation.

(Choices D and E) Lines D and E are shifted to the right, indicating a low oxygen affinity hemoglobin. Hemoglobin A has low affinity for oxygen under conditions such as decreased pH, increased temperature, and increased 2,3-diphosphoglycerate.

Educational objective:
The individual subunits of the hemoglobin molecule are structurally analogous to myoglobin. If separated, the monomeric subunits will demonstrate a hyperbolic oxygen-dissociation curve similar to that of myoglobin.

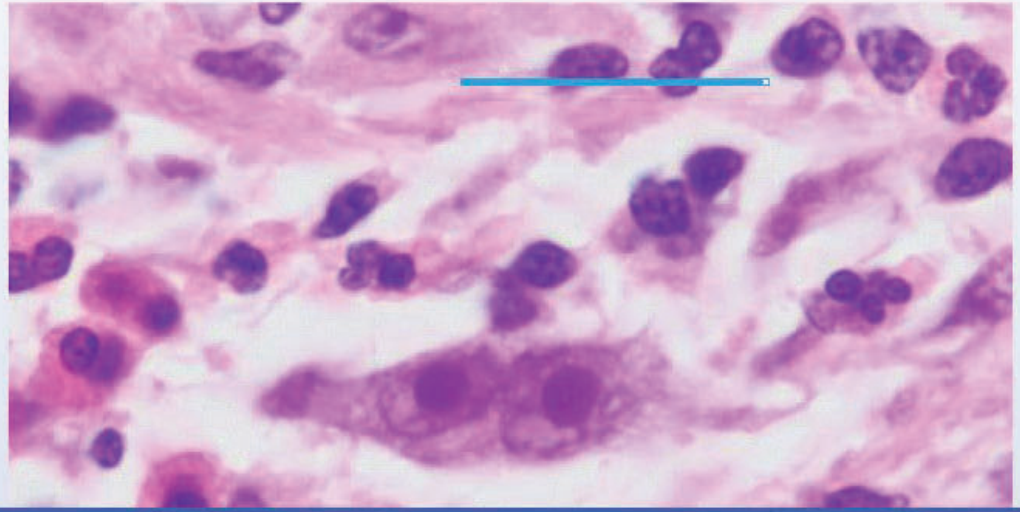
References

- Myoglobin oxygen dissociation by multiwavelength spectroscopy.

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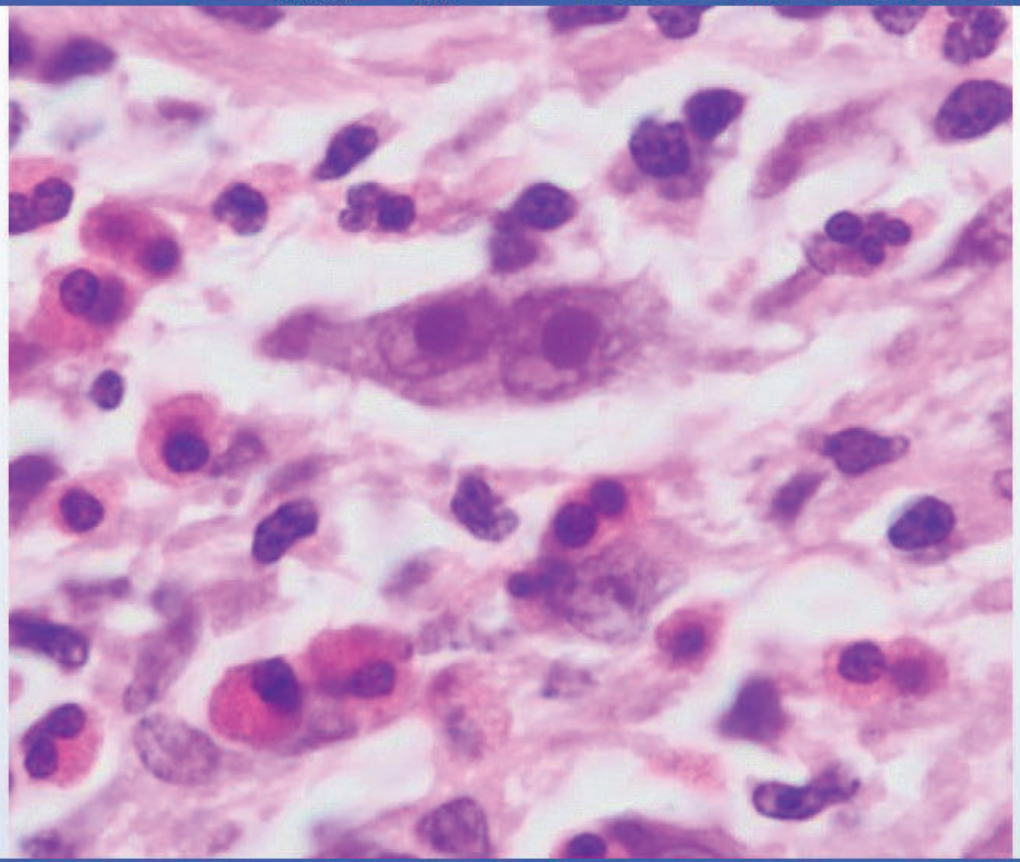
www.ncbi.nlm.nih.gov/pubmed/18413611

A 28-year-old previously healthy man comes to the office due to episodic fevers, night sweats, and weight loss for several months. He emigrated from Kenya with his family at age 14. He does not use tobacco, alcohol, or illicit drugs. The patient works as a driving instructor and volunteers at a homeless shelter. His temperature is 37.2 C (99 F). Physical examination is normal with the exception of cervical lymphadenopathy. A lymph node biopsy is performed, and histopathologic findings are shown in the image below.

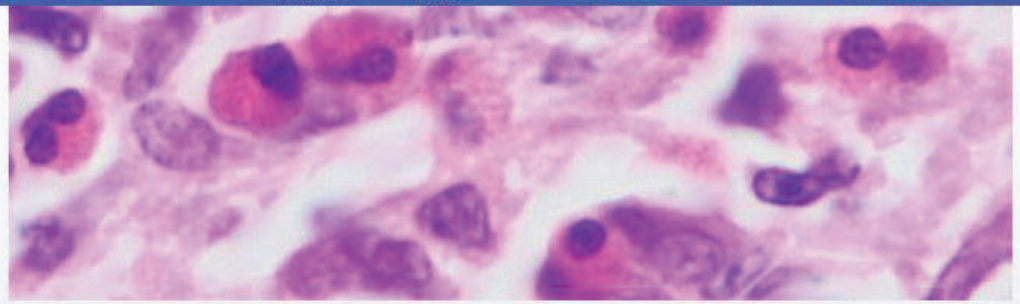


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Which of the following is the most likely diagnosis?

- A. Burkitt lymphoma
- B. Follicular lymphoma
- C. Hodgkin lymphoma
- D. Large B-cell lymphoma
- E. Multiple myeloma
- F. Tuberculosis

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An 8-year-old boy is brought to the emergency department due to 24 hours of fever and chills. Temperature is 38.3 C (101 F). On examination, the patient is lethargic with dry mucous membranes. There are no oropharyngeal lesions, and tympanic membranes are normal. The lungs are clear on auscultation, and heart sounds are normal. The abdomen is soft and nontender. There is no skin rash. Laboratory testing shows a leukocyte count of 24,000/mm^3 with 15% bands, 80% neutrophils, and 5% lymphocytes. Peripheral blood smear is shown in the exhibit. Blood cultures are obtained and intravenous fluids and empiric antibiotics are initiated. The patient's blood cultures are most likely to grow which of the following organisms?

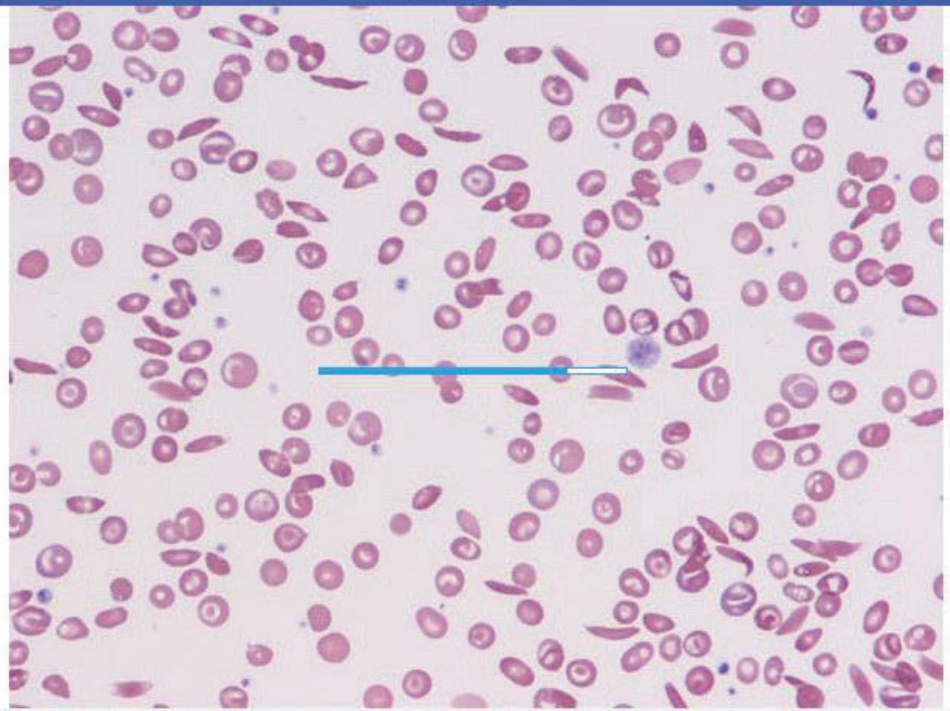
A. *Escherichia coli*
B. *Pseudomonas aeruginosa*
C. *Staphylococcus aureus*
D. *Streptococcus pneumoniae*
E. *Streptococcus pyogenes*
F. Viridans streptococci

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temperature is 38.3°C (101°F). On examination, the patient is lethargic with dry mucous membranes.

Exhibit Display



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Proceed to Next Item

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A 24-year-old African American woman comes to the office with her husband for prenatal counseling. She has a 3-year-old child with sickle cell anemia from a previous marriage, and the child's father died in a car accident. The patient remarried last year and is interested in having more children. She and her new husband do not have sickle cell anemia, and the patient's husband has no other children. However, the patient and her husband are worried that their future children could have sickle cell anemia. A urine pregnancy test is negative. Which of the following is the best initial test that can be offered to this couple?

A. Chorionic villous sampling during future pregnancy
B. Maternal hemoglobin electrophoresis
C. Northern blot analysis of paternal blood sample
D. Paternal hemoglobin electrophoresis
E. Paternal karyotype analysis

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A 7-year-old boy is admitted to the hospital after his adoptive parents brought him to the emergency department due to fatigue and pallor. Laboratory evaluation reveals pancytopenia with an absolute neutrophil count consistent with severe neutropenia. Bone marrow examination reveals signs of aplastic anemia, and subsequent genetic testing reveals a congenital genomic defect in DNA repair leading to chromosomal instability. A bone marrow transplant is required for treatment. The patient's only living relatives are an identical twin brother and older sister who were both adopted by the same parents. He also has stored umbilical stem cells that were harvested after birth. Which of the following is the best bone marrow transplantation method for this patient?

A. Freshly harvested autologous transplant
B. Matched unrelated donor
C. Stored umbilical cord stem cells from the patient
D. Twin sibling syngenetic transplant
E. Unmatched sibling allogeneic transplant

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A 12-year-old boy has prolonged oral bleeding immediately after a tooth extraction. Despite several interventions, the bleeding persists for hours and stops only after desmopressin (DDAVP) administration. The patient has several dental caries due to excessive juice intake and inconsistent oral hygiene. He has no other medical problems and takes no medications. His father and paternal grandmother have also had excessive bleeding after dental procedures. Review of systems is positive for mild bruising on his legs. Which of the following is the most likely therapeutic mechanism of desmopressin for this patient's condition?

A. Binding to renal tubular cell receptors
B. Increase in endothelial protein release
C. Increase in liver protein synthesis
D. Inhibition of fibrinolysis
E. Vascular smooth muscle contraction

Proceed to Next Item

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A 45-year-old man comes to the office for evaluation of fatigue that has been gradually increasing over the past 4 months. The patient has had difficulty keeping up with the labor involved with his job as a construction worker. Over the past 2 weeks, he has been unable to climb past the second floor of the building his company is renovating. The patient also has increasing shortness of breath with minor activities, such as lifting his toolbox out of the car. Review of systems reveals constipation and decreased concentration. Physical examination shows an overweight male with conjunctival pallor who has difficulty getting onto the examination table due to shortness of breath. Laboratory test results are as follows:

Complete blood count	
Hematocrit	26%
Mean corpuscular volume	72 fL
Ferritin	50 ng/mL (normal: 15-200 ng/mL)
Iron studies	
Iron	120 µg/dL (normal: 60-160 µg/dL)
Iron binding capacity	320 ug/dL (normal: 250-460 ug/dL)

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Ferritin	50 ng/mL (normal: 15-200 ng/mL)
Iron studies	
Iron	120 µg/dL (normal: 60-160 µg/dL)
Iron binding capacity	320 µg/dL (normal: 250-460 µg/dL)

Which of the following findings would most likely be seen on this patient's peripheral blood smear?

A. Basophilic stippling
B. Heinz bodies
C. Howell-Jolly bodies
D. Ring sideroblasts
E. Schistocytes

Proceed to Next Item

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A 6-year-old boy is brought to the emergency department due to bleeding after a dental extraction earlier this morning. The patient's past medical history is significant for painful swelling of his knee joints after minor trauma. Aspiration of the joints during several occasions yielded frank blood, and he was diagnosed with hemarthrosis. He has no known allergies. Currently, hemostasis in this patient most likely can be achieved by the administration of which of the following?

- A. Factor XII
- B. Fibrinogen
- C. Protein C
- D. Thrombin
- E. Urokinase

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A 34-year-old man is brought to the hospital by ambulance after being involved in a motor vehicle collision. He was an unrestrained passenger and sustained considerable trauma. On arrival to the emergency department, he is hypotensive and bleeding from several sites. The patient receives an emergency blood transfusion as part of the resuscitation efforts. Abdominal ultrasound reveals splenic laceration and blood in the peritoneal cavity. En route to the operating room, the patient develops difficulty breathing, chills, and pain in the chest and back. Urine drainage from the Foley catheter was initially clear but now appears brown in color. Which of the following is the most likely cause of this patient's new findings?

A. $CD8^+$ lymphocyte-mediated cytotoxicity
B. Complement-mediated cell lysis
C. Endotoxin-induced TNF-α surge
D. IgE-mediated reaction to serum proteins
E. Vascular deposition of immune complexes

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An infant born to a Greek immigrant appears healthy at birth but develops transfusion-dependent hemolytic anemia by the age of 6 months. His erythrocytes contain insoluble aggregates of hemoglobin subunits. The child developed normally in utero because at that time he produced high quantities of:

A. α-globin
B. β-globin
C. γ-globin
D. δ-globin
E. ζ-globin

Proceed to Next Item

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A 65-year-old man comes to the office due to several months of severe fatigue that limits his ability to do daily activities. He has also had upper abdominal fullness, early satiety, and unintentional weight loss but no fever, night sweats, cough, or rash. The patient has not seen a physician for many years. He does not use tobacco, alcohol, or illicit drugs and is a retired chemical engineer. Physical examination shows mucosal pallor with no scleral icterus. The lungs are clear on auscultation, and heart sounds are normal. There is mild hepatomegaly, and the spleen tip is palpable close to the midline of the abdomen. Laboratory evaluation reveals pancytopenia. Peripheral blood smear shows immature granulocytes, nucleated erythrocytes, and teardrop cells. Bone marrow aspiration is attempted but yields no marrow. Which of the following histopathological features is most likely to be present in this patient's spleen?

A. Accumulation of macrophages with fibrillary cytoplasm
B. Diffuse neutrophilic infiltration and follicular necrosis
C. Dilated sinusoids and fibrous nodules with hemosiderin
D. Large islands of hematopoietic progenitor cells
E. Numerous noncaseating epithelioid granulomas

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A 34-year-old industry worker experiences rapid-onset shortness of breath, dizziness, palpitations, and flushed skin after accidental exposure to chemical fumes. Examination by an occupational physician shows that the patient is tachypneic and has a reddish discoloration of the skin without cyanosis. The patient is immediately instructed to inhale amyl nitrite from the safety kit. The success of this antidote is dependent upon its ability to convert hemoglobin into a form with increased affinity for which of the following substances?

A. 2,3-biphosphoglycerate
B. Carbon dioxide
C. Carbon monoxide
D. Cyanide
E. Iron
F. Lead

Proceed to Next Item

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A 24-year-old man comes to the clinic due to 2 weeks of progressive generalized weakness. He has also had significant bruising on his trunk that developed spontaneously without trauma. The patient has no known medical conditions and takes no medications. Temperature is 37.1 C (98.8 F), pulse is 120/min, and respirations are 20/min. Conjunctival pallor is present. Cardiac examination reveals mild sinus tachycardia with no murmurs. Skin examination shows truncal ecchymoses but is otherwise normal. Laboratory results reveal a hemoglobin of 6.8 g/dL and a normal creatinine. Bone marrow aspiration is grossly pale and histologically appears diluted due to high lipid content. Which of the following laboratory patterns is most likely present in this patient?

	Erythropoietin	Reticulocytes	Mean corpuscular volume	Haptoglobin
A.	↑	↑	Normal	Low
B.	↑	↓	Normal	Normal
C.	↑	↓	↓	High

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with no murmurs. Skin examination shows truncal ecchymoses but is otherwise normal. Laboratory results reveal a hemoglobin of 6.8 g/dL and a normal creatinine. Bone marrow aspiration is grossly pale and histologically appears diluted due to high lipid content. Which of the following laboratory patterns is most likely present in this patient?

	Erythropoietin	Reticulocytes	Mean corpuscular volume	Haptoglobin
A.	↑	↑	Normal	Low
B.	↑	↓	Normal	Normal
C.	↑	↓	↓	High
D.	↓	↑	↓	Low
E.	↓	↓	Normal	Normal

Proceed to Next Item

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A 5-year-old girl is brought to the emergency department for evaluation of a rash. Her mother noticed a few red spots on the child's cheeks this morning, which subsequently spread to the neck and trunk as the day progressed. The patient has a history of partial complex seizures, which have been well controlled with carbamazepine. Vital signs are normal. The lips are slightly pale, and the oropharynx is clear. There is no lymphadenopathy. The abdomen is soft with no palpable masses or hepatosplenomegaly. Skin examination shows flat, red, pinpoint lesions that do not blanch on the face, neck, trunk, and extremities. Neurological examination is unremarkable. Laboratory results are as follows:

Complete blood count

Hemoglobin	9.5 g/dL
Platelets	25,000/mm^3
Leukocytes	2,900/mm^3

Peripheral smear reveals a paucity of cells with normal morphologic appearance of all cell lines. Which of the following mechanisms is most likely responsible for this patient's current condition?

A. Autoantibodies against hematopoietic stem cells

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Complete blood count

Hemoglobin	9.5 g/dL
Platelets	25,000/mm^3
Leukocytes	2,900/mm^3

Peripheral smear reveals a paucity of cells with normal morphologic appearance of all cell lines. Which of the following mechanisms is most likely responsible for this patient's current condition?

A. Autoantibodies against hematopoietic stem cells
B. Impaired DNA synthesis due to vitamin deficiency
C. Medication-associated adverse effect
D. Peripheral cell sequestration in splenic sinusoids
E. Thrombotic microangiopathic hemolysis

Proceed to Next Item

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A 54-year-old woman comes to the office due to 3 months of progressive pain and prolonged morning stiffness in her hand joints. She has tried over-the-counter naproxen without significant relief. Review of systems is positive for fatigue. The patient has no other chronic medical conditions and takes no other medications regularly. Vital signs are normal. Swelling and tenderness of the proximal interphalangeal joints and metacarpophalangeal joints are present in both hands. Laboratory studies reveal a hemoglobin of 9.8 g/dL and MCV of 86. The patient is prescribed methotrexate therapy. Laboratory results 6 months later reveal that hemoglobin has increased to 12 g/dL. If measured, which of the following changes were most likely present in this patient before the start of methotrexate therapy?

	Circulating iron level	Bone marrow iron
A.	Low	High
B.	Low	Low
C.	High	Low
D.	High	High

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medications regularly. Vital signs are normal. Swelling and tenderness of the proximal interphalangeal joints and metacarpophalangeal joints are present in both hands. Laboratory studies reveal a hemoglobin of 9.8 g/dL and MCV of 86. The patient is prescribed methotrexate therapy. Laboratory results 6 months later reveal that hemoglobin has increased to 12 g/dL. If measured, which of the following changes were most likely present in this patient before the start of methotrexate therapy?

	Circulating iron level	Bone marrow iron
A.	Low	High
B.	Low	Low
C.	High	Low
D.	High	High
E.	Normal	Low
F.	High	Normal

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order. Once you click **Proceed to Next Item**, you will not be able to add or change an answer.

A 24-year-old woman is being evaluated for chronic fatigue. She has a history of heavy menstrual periods since menarche and also recalls frequent nosebleeds as a child. Her past medical history is otherwise insignificant and she takes no medications. Laboratory studies show a hemoglobin level of 9.2 g/dL, a mean corpuscular volume of 72 fL, and decreased levels of ferritin.

Item 1 of 2

Which of the following is the most likely diagnosis?

A. Antiphospholipid syndrome
B. Factor VIII deficiency
C. Factor XIII deficiency
D. Immune thrombocytopenia
E. Protein C deficiency
F. von Willebrand factor deficiency

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Item 2 of 2

Further evaluation shows decreased von Willebrand factor activity in the patient's serum. This protein normally binds to which of the following?

A. Collagen
B. Fibrin polymer
C. Prostacyclin
D. Protein C
E. Thrombin

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A 5-year-old boy is brought to the emergency department due to an hour of epistaxis after he was elbowed in the face during a basketball game. He has a history of prolonged bleeding from the gums after brushing his teeth. Vital signs are normal. The patient has scattered bruises along his arms and legs. He receives desmopressin, which stops the bleeding. This treatment most likely improved the patient's condition through which of the following therapeutic mechanisms?

A. Binds to antidiuretic hormone receptors
B. Increases circulating factor IX
C. Increases circulating von Willebrand factor
D. Increases platelet count
E. Increases vitamin K–dependent coagulation factors
F. Relaxes vascular smooth muscle cells

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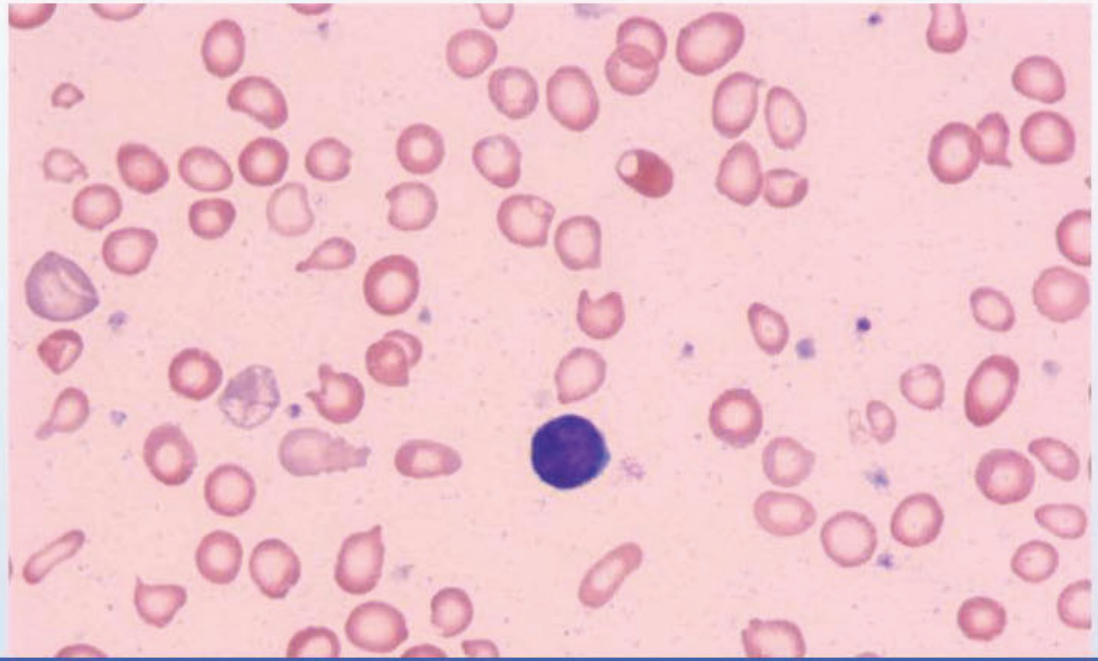
A 66-year-old woman is brought to the emergency department due to left leg pain. Five days ago, the patient underwent elective right hip arthroplasty for advanced osteoarthritis. She had been recovering well at an acute rehabilitation facility until she woke today with severe left calf pain and swelling. The patient has taken daily subcutaneous, low-molecular-weight heparin and as-needed acetaminophen since the surgery. She has no other medical conditions. Temperature is 37 C (98.6 F), blood pressure is 130/70 mm Hg, and pulse is 92/min. The surgical incision over her right hip is healing well. Her left posterior calf is tender and swollen to the knee. Three days ago, complete blood count was normal, but platelet count is now 70,000/mm^3. Peripheral blood smear shows decreased platelet number but no other abnormalities. Which of the following is the most likely cause of this patient's thrombocytopenia?

A. Decreased bone marrow platelet production
B. Mechanical destruction of platelets
C. Non–immune-mediated platelet clumping
D. Platelet removal by splenic macrophages
E. Uncontrolled activation of the coagulation cascade

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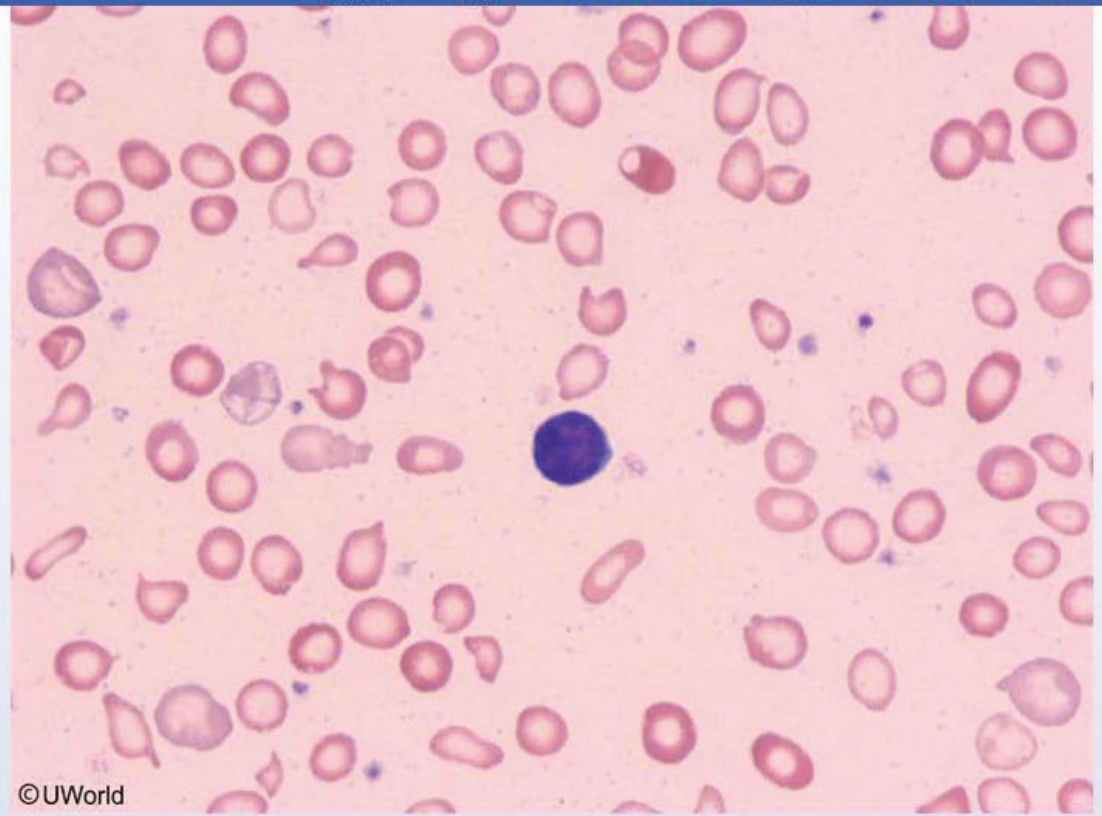
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A 19-year-old woman comes to the office due to exertional dyspnea and intermittent lightheadedness. On examination, mucosal pallor is present. Laboratory studies reveal a red blood cell count of 3.5 million/mm^3 and a hemoglobin concentration of 8.5 g/dL. Peripheral smear is shown in the image below:



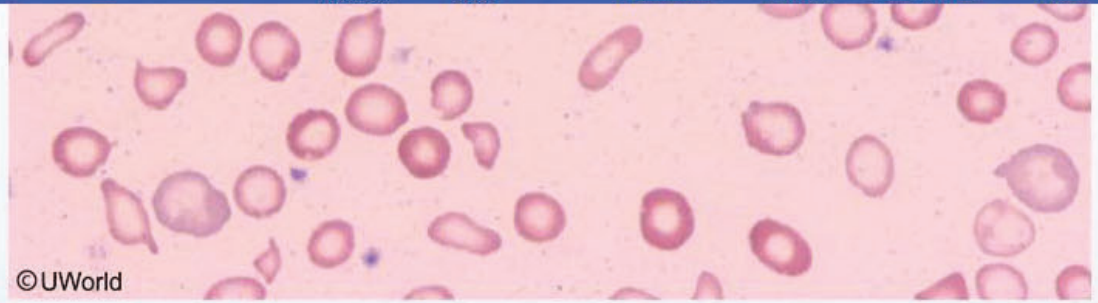
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Which of the following findings are most likely present in this patient?

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Which of the following findings are most likely present in this patient?

A. Decreased transferrin binding capacity
B. Increased macrophage iron retention
C. Increased serum cytokine levels
D. Increased serum erythropoietin levels
E. Increased serum hepcidin levels

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A 48-year-old woman comes to the emergency department with headache, dizziness, and nausea for the past several hours. She has no fever, nasal congestion, or cough but reports that her husband has also been complaining of headache. The patient has been burning wood in the fireplace to warm her house after losing electricity during a snowstorm. Her temperature is 37 C (98.6 F), blood pressure is 135/70 mm Hg, and pulse is 94/min and regular. Physical examination is unremarkable. The substance responsible for this patient's condition most likely impairs hemoglobin function through which of the following mechanisms?

A. Alteration of the partial pressure of oxygen
B. Competitive binding to heme
C. Deactivation of a reductase enzyme
D. Denaturation of the globin chains
E. Irreversible linking to heme
F. Oxidation of the porphyrin ring

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A 56-year-old man comes to the emergency department due to right lower extremity pain and swelling. The symptoms began shortly after he flew back to the United States from a 7-day cruise in Indonesia. Doppler ultrasonography reveals a femoropopliteal venous thrombosis, and the patient is given anticoagulation with rivaroxaban. Compared to vitamin K antagonists, this patient's treatment is most likely to have which of the following benefits?

A. Better patient compliance
B. Greater efficacy
C. Less risk of thrombocytopenia
D. No need for loading dose
E. Less variability in therapeutic effect

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A 62-year-old woman comes to the office due to a month of progressive right chest and back pain. The patient also noticed a right breast lump several months ago, which has grown over time. She has no prior medical issues, has not seen a physician for many years, and has had no cancer screenings. Physical examination reveals a hard, 5-cm right breast mass, enlarged axillary lymph nodes, and point tenderness along the right-sided ribs and 10th thoracic vertebra. Biopsy of the breast mass shows hormone receptor–positive, HER2-negative, invasive ductal carcinoma. Skeletal survey demonstrates lytic lesions of the ribs and thoracic vertebrae. As part of the treatment regimen, the patient receives a medication that is a potent inhibitor of cyclin-dependent kinase. Which of the following is the most likely dose-limiting toxicity of this medication?

A. Bone marrow suppression
B. Cardiomyopathy
C. Immune-mediated toxicity
D. Peripheral neuropathy
E. Sensorineural hearing loss

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A 35-year-old woman comes to the hospital due to sudden-onset numbness in her left arm and face. The patient has had generalized headache, dyspnea on exertion, and easy fatigability for several days but no weakness. She has a history of well-controlled asthma. Temperature is 37.7 C (99.9 F), blood pressure is 110/60 mm Hg, and pulse is 80/min. Light touch sensation is decreased in the left upper extremity and the lower left side of the face. Strength and reflexes are normal. Cardiopulmonary and abdominal examinations are unremarkable. There is no skin rash. Laboratory results are as follows:

Hemoglobin	8.6 g/dL
Platelets	24,000/mm^3
Blood urea nitrogen	32 mg/dL
Creatinine	1.9 mg/dL

PT and PTT are normal. Peripheral blood smear shows numerous schistocytes. Urinalysis is positive for mild proteinuria. Which of the following is the most likely underlying cause of this patient's current condition?

A. IgA immune complex deposition

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Platelets	24,000/mm^3
Blood urea nitrogen	32 mg/dL
Creatinine	1.9 mg/dL

PT and PTT are normal. Peripheral blood smear shows numerous schistocytes. Urinalysis is positive for mild proteinuria. Which of the following is the most likely underlying cause of this patient's current condition?

A. IgA immune complex deposition
B. Impaired cleavage of von Willebrand factor
C. Plasma cell proliferation
D. Rupture of atheromatous plaque
E. Systemic coagulation factor activation

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A 6-year-old girl is brought to the office by her mother due to abdominal pain and vomiting. The patient has Down syndrome but has otherwise been healthy. Abdominal examination reveals the liver edge 3 cm below the costal margin and the spleen tip extending past the level of the umbilicus. Leukocyte count is 104,000/mm^3, and subsequent peripheral blood smear reveals numerous lymphoblasts. The patient is diagnosed with acute lymphoblastic leukemia and combination cytotoxic chemotherapy is planned. Which of the following laboratory changes are most likely to be seen in this patient following treatment initiation?

	Potassium	Uric acid	Phosphorous	Lactate dehydrogenase
A.	↓	↑	↑	↑
B.	↓	↑	↓	↑
C.	↑	↓	↓	↑
D.	↑	↑	↓	↓
E.	↑	↑	↑	↓

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Down syndrome but has otherwise been healthy. Abdominal examination reveals the liver edge 3 cm below the costal margin and the spleen tip extending past the level of the umbilicus. Leukocyte count is 104,000/mm^3, and subsequent peripheral blood smear reveals numerous lymphoblasts. The patient is diagnosed with acute lymphoblastic leukemia and combination cytotoxic chemotherapy is planned. Which of the following laboratory changes are most likely to be seen in this patient following treatment initiation?

	Potassium	Uric acid	Phosphorous	Lactate dehydrogenase
A.	↓	↑	↑	↑
B.	↓	↑	↓	↑
C.	↑	↓	↓	↑
D.	↑	↑	↓	↓
E.	↑	↑	↑	↓
F.	↑	↑	↑	↑

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A 23-year-old woman with a history of sickle cell disease comes to the office for follow-up. The patient is homozygous for hemoglobin S and has had frequent episodes of painful vasoocclusive crises. She has no other medical conditions and takes folic acid supplementation. The patient does not use tobacco, alcohol, or illicit drugs. Physical examination shows no abnormalities. Additional therapy with hydroxyurea is planned. This medication is likely to improve this patient's symptoms primarily through which of the following mechanisms?

A. Decreased red blood cell dehydration
B. Direct inhibition of red blood cell polymerization
C. Increased hemoglobin A2 synthesis
D. Increased fetal hemoglobin synthesis
E. Increased red blood cell antioxidant levels
F. Stimulation of red blood cell production

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In vitro studies demonstrate that tumor cell lines can become resistant after exposure to various anticancer agents. These cells express a specific cell surface glycoprotein that has which of the following functions?

A. Tyrosine kinase-coupled receptor
B. Adenylate cyclase-coupled receptor
C. Cell adhesion molecule
D. Transmembrane ion channel
E. ATP-dependent transporter

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A 20-year-old man is evaluated for recurrent episodes of jaundice. He was separated from his parents at a young age and is unaware of any family medical history. The patient resided in several foster homes throughout his childhood but currently lives alone. His temperature is 36.7 C (98 F), blood pressure is 120/80 mm Hg, and pulse is 72/min. Physical examination shows pallor, icterus, and mild splenomegaly. There is no lymphadenopathy or hepatomegaly. The remainder of the physical examination is normal. Laboratory test results are as follows:

Hemoglobin	9 g/L
Platelets	198,000/mm^3
Leukocytes	6500/mm^3
Lactate dehydrogenase	Increased
Total bilirubin	3.4 mg/dL
Direct bilirubin	0.2 mg/dL
Aspartate aminotransferase (AST)	25 U/L

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Leukocytes	6500/mm^3
Lactate dehydrogenase	Increased
Total bilirubin	3.4 mg/dL
Direct bilirubin	0.2 mg/dL
Aspartate aminotransferase (AST)	25 U/L
Alanine aminotransferase (ALT)	30 U/L
Direct Coombs test	Negative

When the patient's red blood cells are incubated in a hypotonic solution with glycerol, hemoglobin is released. The control sample does not release hemoglobin. This patient is at greatest risk of developing which of the following?

A. Autoimmune disease

B. Autoinfarction of the spleen

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aminotransferase (AST)	
Alanine aminotransferase (ALT)	30 U/L
Direct Coombs test	Negative

When the patient's red blood cells are incubated in a hypotonic solution with glycerol, hemoglobin is released. The control sample does not release hemoglobin. This patient is at greatest risk of developing which of the following?

A. Autoimmune disease
B. Autoinfarction of the spleen
C. Avascular necrosis of the femur
D. Hemolysis from consumption of fava beans
E. Pigmented gallstones

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A 42-year-old man is hospitalized with fever and persistent sore throat. On physical examination, his temperature is 38.3 C (101 F), blood pressure is 120/80 mm Hg, pulse is 94/min, and respirations are 16/min. There are several bruises on his trunk, and blood is oozing from his intravenous catheter venipuncture sites. His blood fibrinogen level is 110 mg/dL (normal 150-400 mg/dL). Bone marrow biopsy shows a predominance of immature myeloid cells with azurophilic needle-shaped cytoplasmic granules. Chromosomal analysis of these immature cells is most likely to show which of the following abnormalities?

- A. t(8;14)
- B. t(9;22)
- C. t(14;18)
- D. t(15;17)
- E. inv(16)

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A 13-month-old boy is brought to the clinic after repeated infections for the past 4 months, including otitis media, pneumonia, and erysipelas. Although his infections have been responsive to treatment, his father is concerned about the number of infections. The patient also has persistent diarrhea, and a recent stool antigen detection assay was positive for *Giardia lamblia*. An immunoglobulin panel demonstrates very low serum levels of all immunoglobulin types. Intradermal injection of *Candida* antigens results in a large indurated nodule within 48 hours. This patient's lymph nodes most likely lack which of the following structures?

- A. Germinal centers
- B. Outer cortex
- C. Paracortical zone
- D. Subcapsular sinuses
- E. Trabeculae

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A 9-year-old boy with beta thalassemia major comes to the office for a routine red blood cell transfusion. He was diagnosed at age 6 months and has since received numerous blood transfusions and chelation therapies. The patient has tolerated each transfusion and chelation therapy well with no immediate reactions or side effects. Vital signs are normal. On physical examination, the boy has mild frontal bossing, hepatosplenomegaly, and jaundice. A recent liver biopsy showed Kupffer cells containing coarse, yellowish-brown cytoplasmic granules. The granules are most likely composed of which of the following?

- A. Amyloid
- B. Bilirubin
- C. Copper
- D. Glycogen
- E. Glycolipid
- F. Hemosiderin
- G. Lipofuscin

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A 66-year-old man with hypertension and stage IV chronic kidney disease comes to the office for follow-up. The patient has had worsened fatigue and low energy over the past several months but no chest pain or shortness of breath. He was previously nonadherent with antihypertensive therapy but has been following treatment recommendations since renal dysfunction was diagnosed 2 years ago. Blood pressure is 126/78 mm Hg and pulse is 68/min. Cardiac auscultation reveals an S4 sound. The rest of the physical examination is unremarkable. Laboratory results show normocytic, normochromic anemia with a low reticulocyte count. Serum iron studies are within normal limits. Treatment with a recombinant glycoprotein hormone is begun, and repeat laboratory testing several weeks later shows an improvement in hemoglobin level. The effects of the hormone prescribed for this patient are most likely mediated by which of the following pathways?

A. Adenylate cyclase/cyclic AMP

B. Arachidonic acid/phospholipase A2

C. Janus kinase 2/signal transducers and activators of transcription

D. Nuclear receptors

E. Phosphatidylinositol 3-kinase

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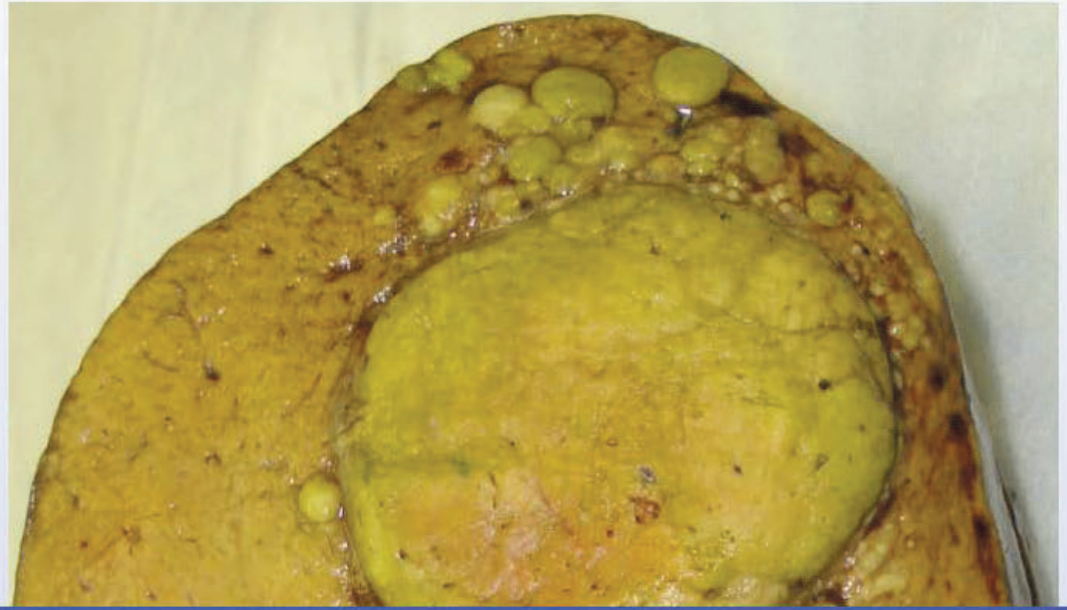
treatment recommendations since renal dysfunction was diagnosed 2 years ago. Blood pressure is 126/78 mm Hg and pulse is 68/min. Cardiac auscultation reveals an S4 sound. The rest of the physical examination is unremarkable. Laboratory results show normocytic, normochromic anemia with a low reticulocyte count. Serum iron studies are within normal limits. Treatment with a recombinant glycoprotein hormone is begun, and repeat laboratory testing several weeks later shows an improvement in hemoglobin level. The effects of the hormone prescribed for this patient are most likely mediated by which of the following pathways?

- A. Adenylate cyclase/cyclic AMP
- B. Arachidonic acid/phospholipase A2
- C. Janus kinase 2/signal transducers and activators of transcription
- D. Nuclear receptors
- E. Phosphatidylinositol 3-kinase
- F. Ras/mitogen-activated protein kinase

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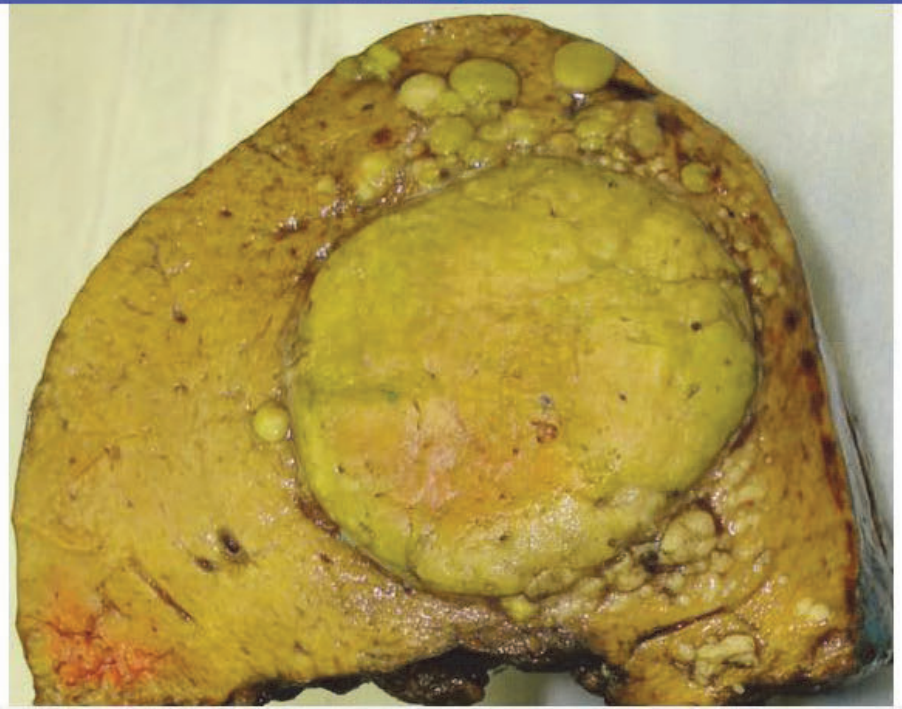
A 64-year-old man is brought to the hospital by ambulance after being found unresponsive by his brother. Despite resuscitative efforts, he dies shortly thereafter. The family reports that the patient had 2 months of progressive fatigue and an unintentional weight loss prior to the episode. Autopsy examination reveals a massive pulmonary embolus, and a cross-section of the liver shows the following:



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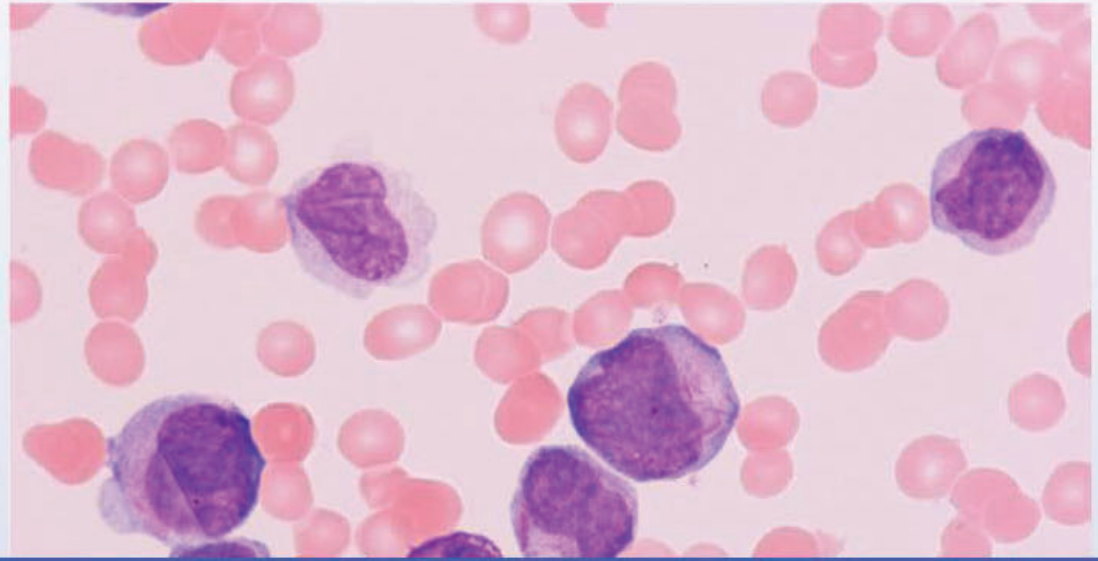
Genomic analysis of the hepatic lesions demonstrates intranuclear fragments of foreign DNA. These fragments most likely belong to which of the following pathogens?

A. Cytomegalovirus
B. *Entamoeba histolytica*
C. Epstein-Barr virus
D. Hepatitis B virus
E. Hepatitis C virus
F. Human papilloma virus

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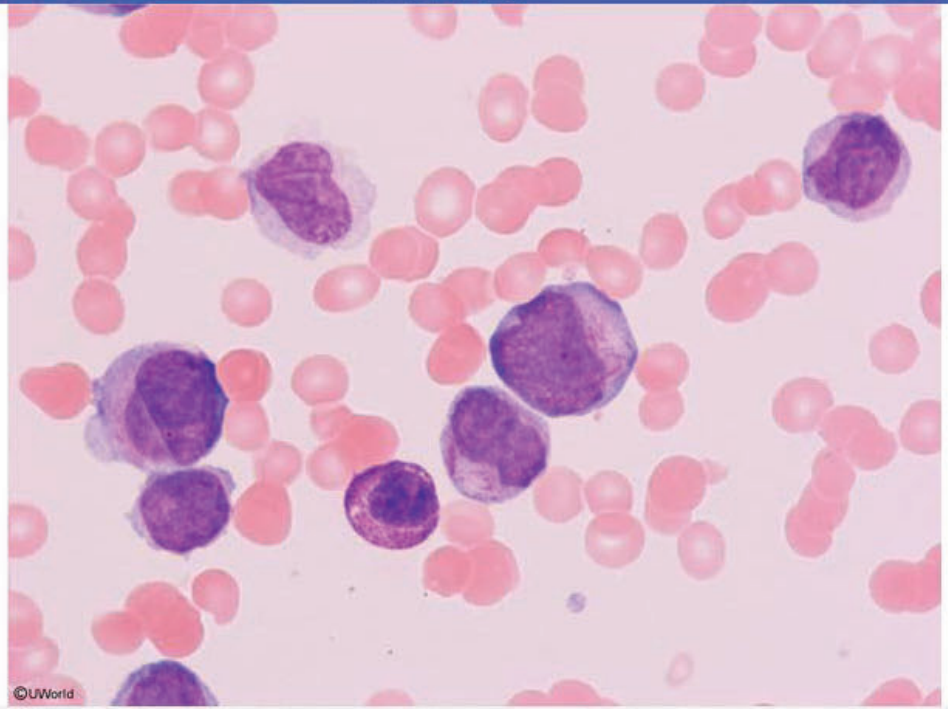
A 43-year-old man comes to the hospital due to recurrent episodes of fever and sore throat despite multiple courses of antibiotic therapy. For the past several months, he has also felt "run down" and fatigued all the time. His wife adds that he bruises easily and has had bleeding gums on several occasions. His temperature is 37.8 C (100.2 F). On examination, he has mucosal pallor, pharyngeal erythema, and multiple ecchymoses on his extremities. His peripheral blood smear is shown in the image below.



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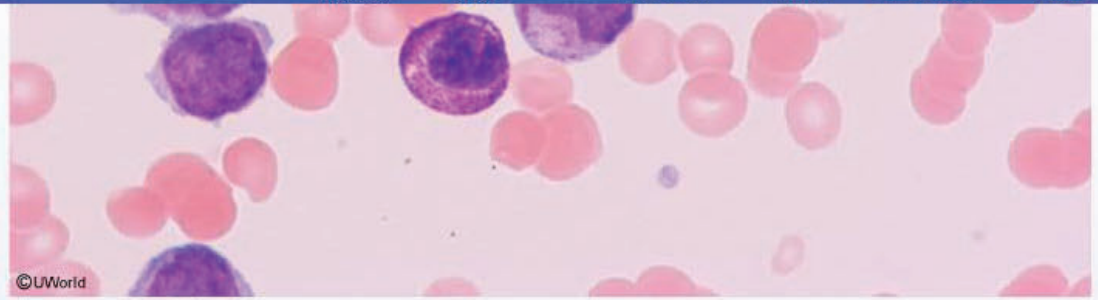
temperature is 37.8 C (100.2 F). On examination, he has mucosal pallor, pharyngeal erythema, and

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Which of the following chromosomal abnormalities is most likely present in the affected cells?

- A. t(8;14)
- B. t(9;22)
- C. t(11;14)
- D. t(15;17)
- E. 13q-

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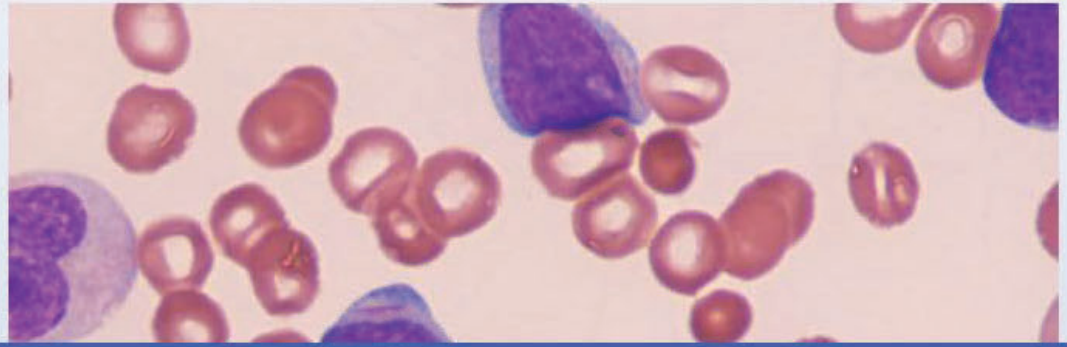
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A 63-year-old man comes to the office due to fatigue and easy bruising. He has no lymphadenopathy on physical examination. Laboratory results are as follows:

Complete blood count

Hemoglobin	8.0 g/dL
Platelets	40,000/mm^3
Leukocytes	20,500/mm^3

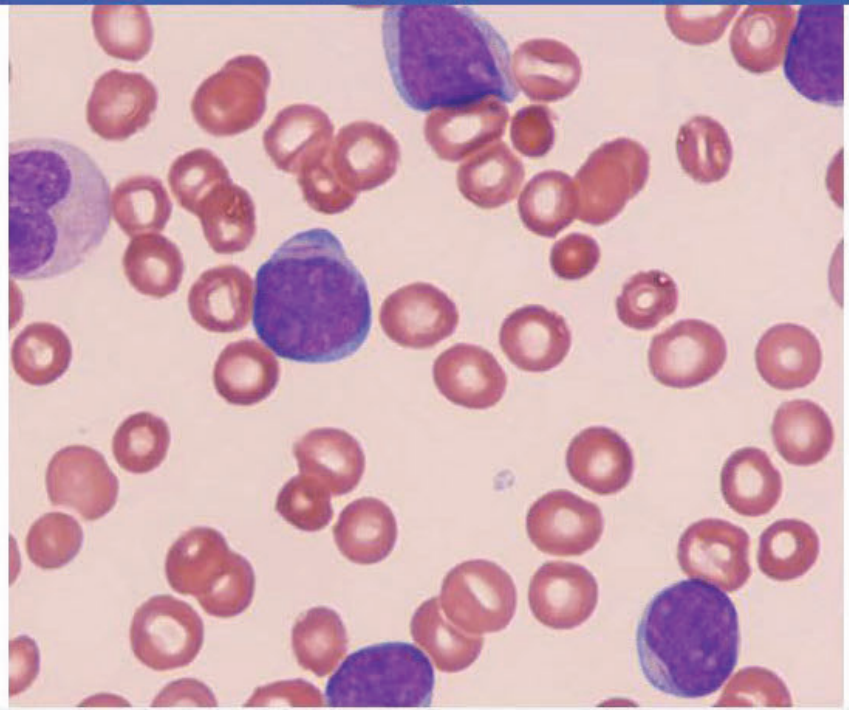
The patient's peripheral blood smear is shown in the image below:



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Which of the following is the most likely diagnosis?

A. Acute lymphoblastic leukemia
B. Acute myelogenous leukemia
C. Chronic lymphocytic leukemia
D. Chronic myelogenous leukemia
E. Hairy cell leukemia
F. Hodgkin lymphoma
G. Infectious mononucleosis

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A 24-year-old, previously healthy woman comes to the hospital due to a 3-day history of fever, dyspnea, and cough productive of yellow sputum. Temperature is 38.8 C (101.8 F), blood pressure is 110/66 mm Hg, and pulse is 110/min. The patient has bronchial breath sounds and crackles over the right lower lung. Laboratory results are as follows:

Hemoglobin	13 g/dL
Platelets	350,000/mm^3
Leukocytes	54,000/mm^3
Neutrophils	65%
Band forms	10%
Myelocytes	3%
Metamyelocytes	1%
Lymphocytes	15%

The leukocyte alkaline phosphatase test score is elevated. Which of the following is the most likely finding

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Band forms	10%
Myelocytes	3%
Metamyelocytes	1%
Lymphocytes	15%

The leukocyte alkaline phosphatase test score is elevated. Which of the following is the most likely finding on this patient's peripheral blood smear?

A. Basophilic oval inclusions in mature neutrophils
B. Basophilic stippling of red blood cells
C. Mature neutrophils with hypersegmented nuclei
D. Numerous blasts with azurophilic rods
E. Small lymphoid cells with cleaved nuclei

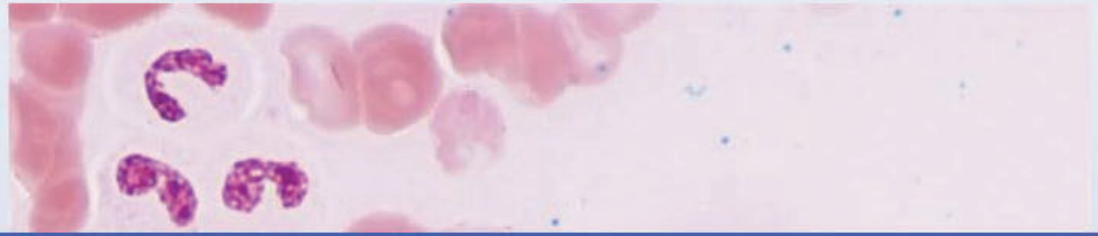
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A 40-year-old woman comes to the office with a 3-month history of progressively limited physical activity due to fatigue. The patient says, "I could barely walk from my car to the office." Medical history is significant for a positive tuberculin skin test 7 months ago with a normal chest radiograph. She has been compliant with the prescribed treatment despite its bitter taste. Physical examination shows a tired-appearing woman with conjunctival and palmar pallor. Complete blood count is as follows:

Hemoglobin	9 g/dL
Hematocrit	28%
Mean corpuscular volume	72 fL

A bone marrow aspirate representative of this patient's disease process is shown below (Prussian blue stain).

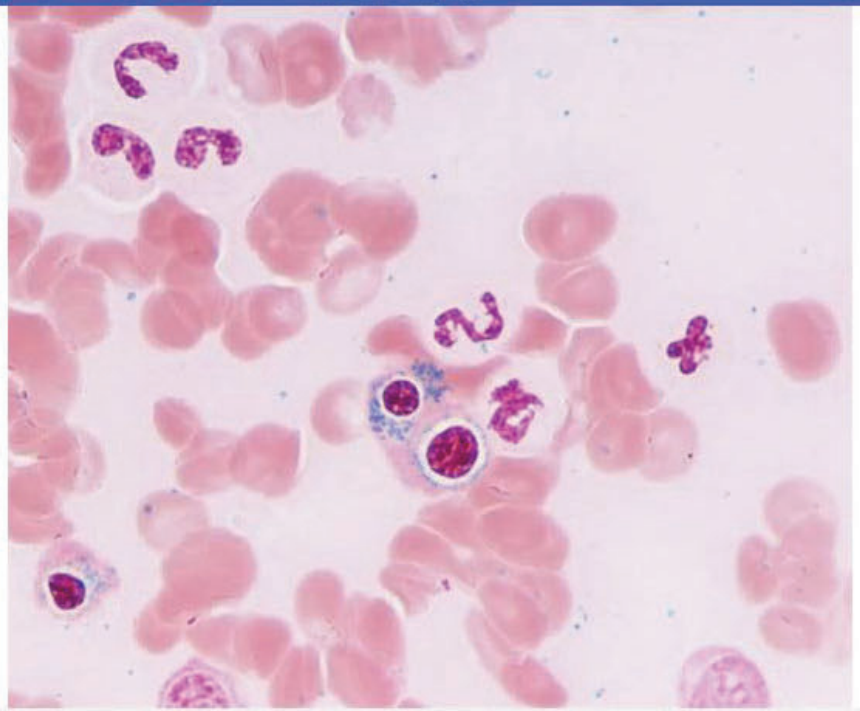


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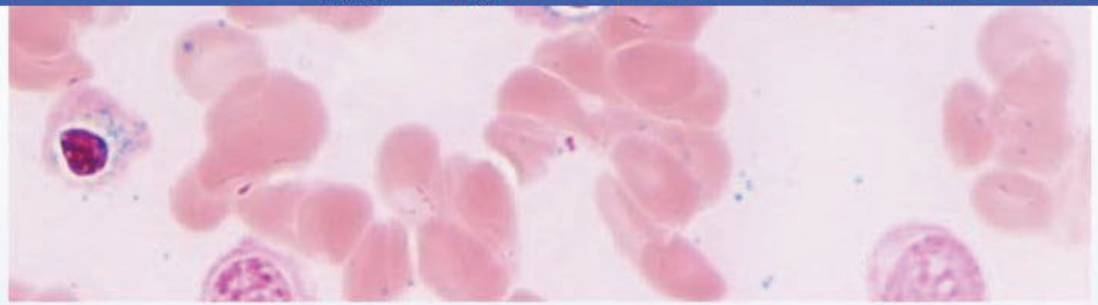
A bone marrow aspirate representative of this patient's disease process is shown below (Prussian blue

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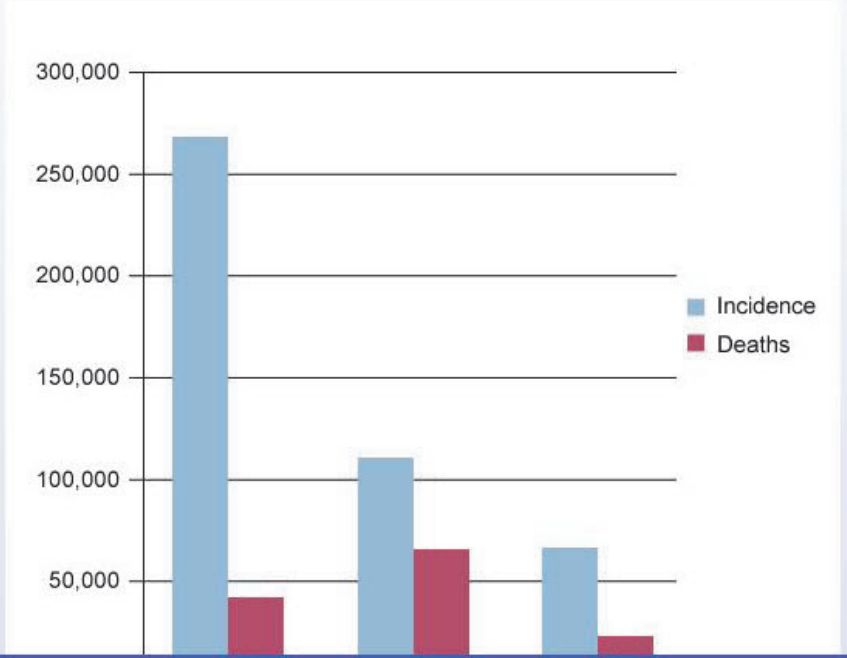
Decreased activity of which of the following enzymes most likely explains the anemia found in this patient?

A. δ-aminolevulinic acid dehydratase
B. δ-aminolevulinic acid synthase
C. Cystathionine synthase
D. Glucose-6-phosphate dehydrogenase
E. Pyruvate kinase

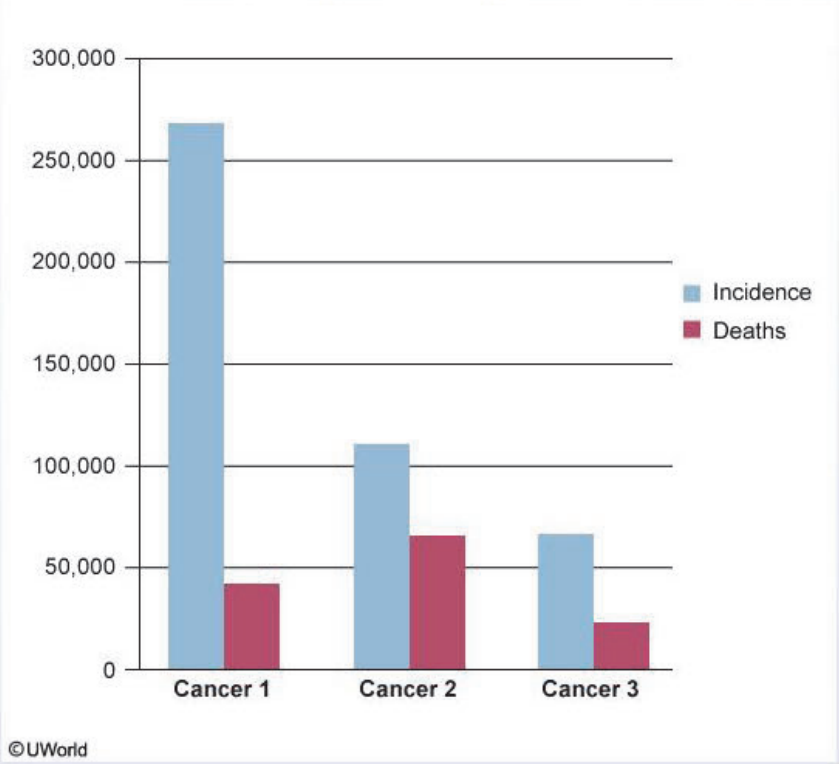
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The figure below shows the estimated incidence and mortality in 2019 for the 3 most common cancers affecting women in the United States, based on the American Cancer Society's *Cancer Facts & Figures 2019*. The x-axis lists the specific cancers, and the y-axis shows the projected number of patients affected.

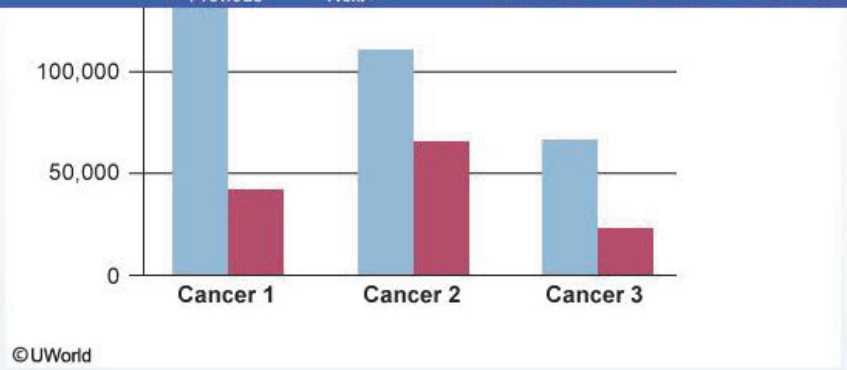


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Which of the following lists of cancers most likely corresponds to Cancers 1, 2, and 3, respectively?

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Which of the following lists of cancers most likely corresponds to Cancers 1, 2, and 3, respectively?

A. Breast, lung, colorectal
B. Lung, breast, colorectal
C. Breast, ovary, lung
D. Lung, breast, cervix
E. Breast, colorectal, lung

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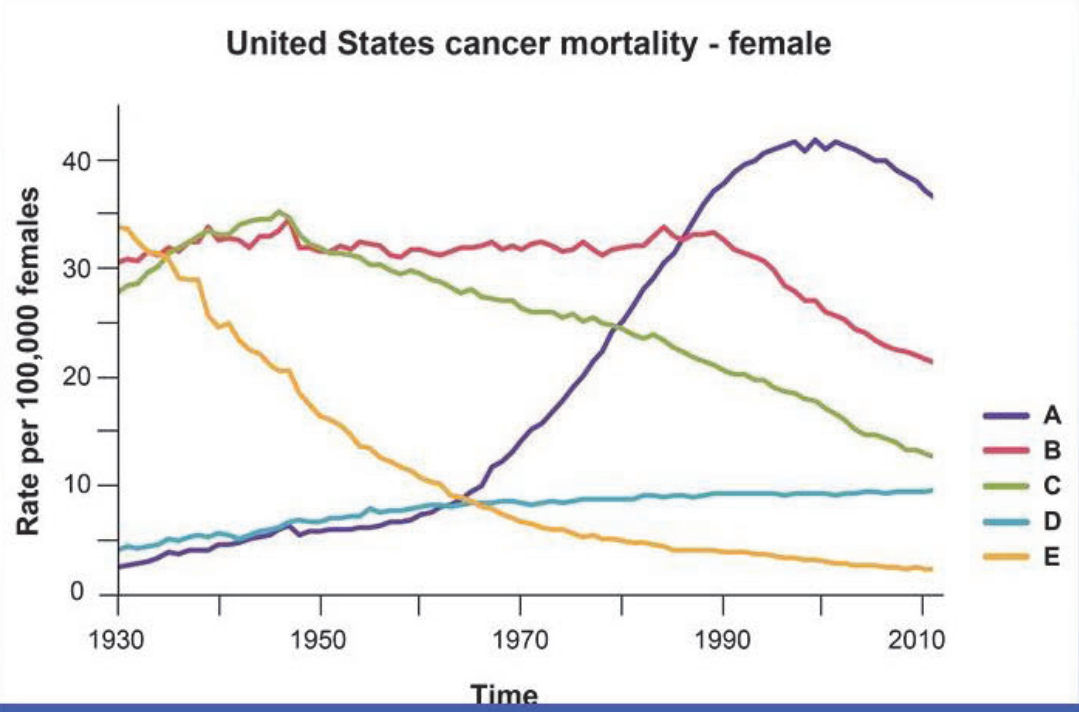
A 45-year-old man comes to the office for progressive weakness and fatigue over the last year. The patient was adopted and does not know his family history. After a comprehensive physical examination and laboratory evaluation, the patient undergoes genetic testing. A loss of expression mutation is identified in a gene coding for a protein found on the basolateral surface of hepatocytes and enterocytes. The protein is known to interact with the transferrin receptor. Which of the following conditions is this patient at greatest risk of developing?

A. Basal ganglia atrophy
B. Fat malabsorption and osteoporosis
C. Iron deficiency anemia
D. Liver cirrhosis and hepatocellular carcinoma
E. Pulmonary emphysema

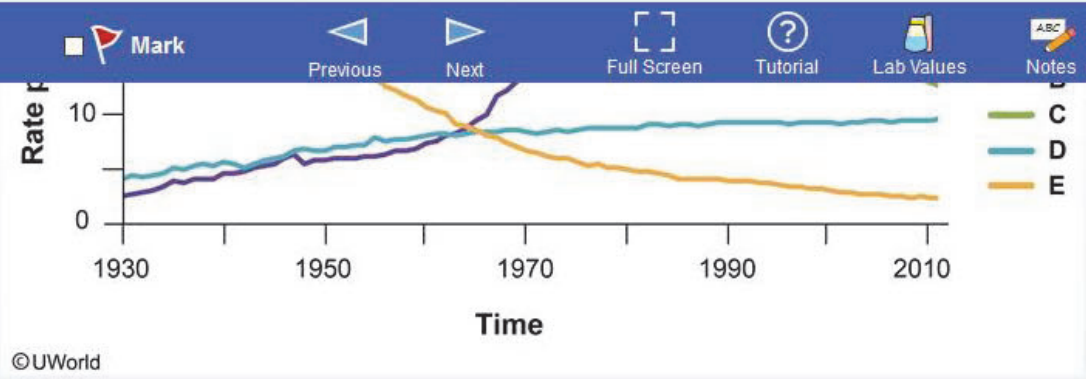
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The age-adjusted mortality trends for 5 cancers in women in the United States are shown in the graph below.



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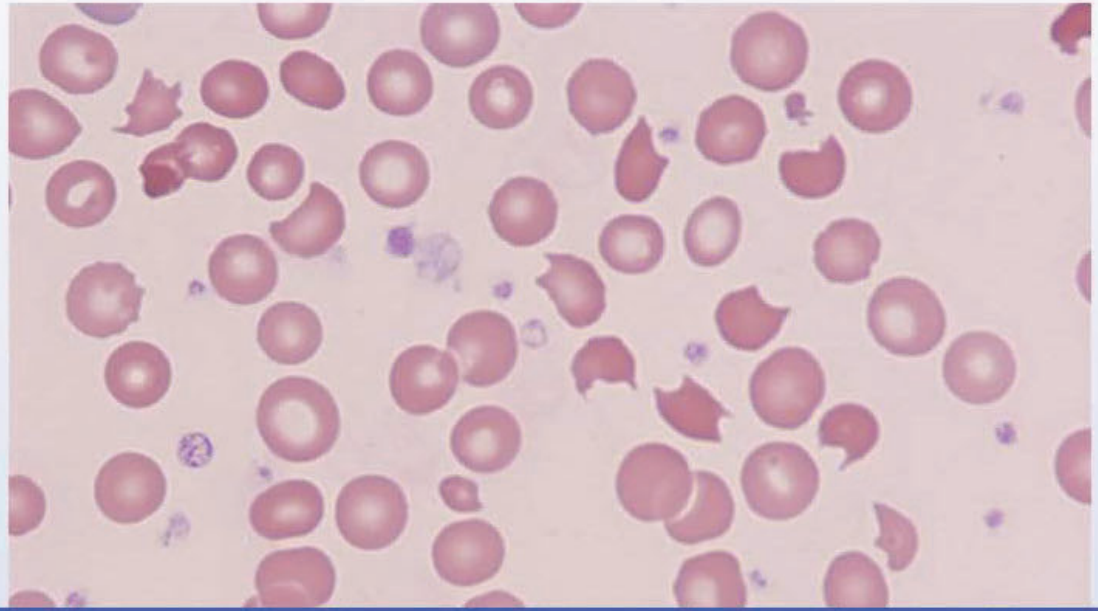
Which of the following curves best corresponds to lung cancer?

- A.A
- B.B
- C.C
- D.D
- E.E

Proceed to Next Item

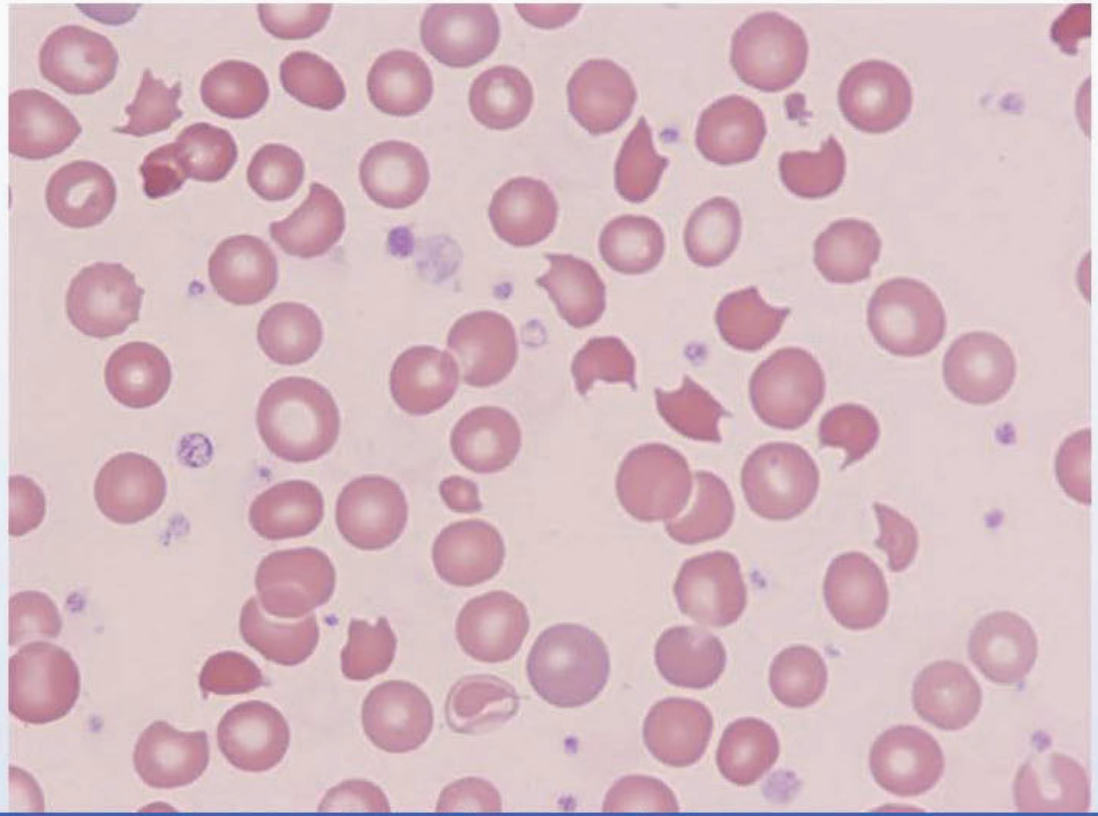
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A 7-year-old boy comes to the office for follow-up. A week ago, the patient began having episodes of bloody diarrhea that have since resolved. His current laboratory studies show elevated blood urea nitrogen and serum creatinine levels. Complete blood count reveals anemia and thrombocytopenia. Coagulation studies are within normal limits. His peripheral blood smear is shown in the image below.

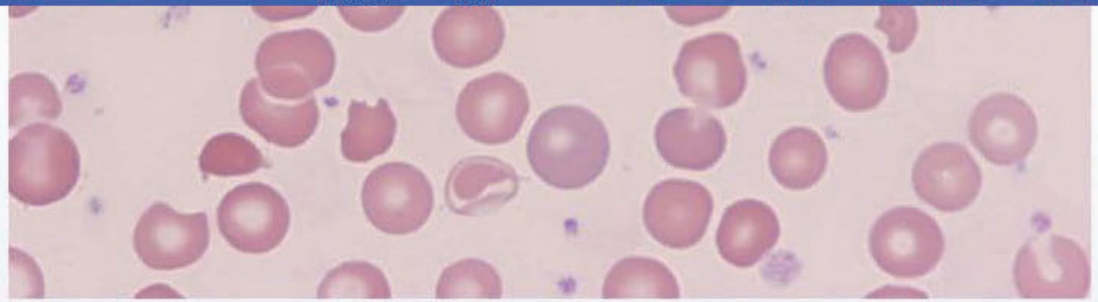


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studies are within normal limits. His peripheral blood smear is shown in the image below:



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Which of the following is the most likely cause of this patient's anemia?

A. Autoimmune hemolytic anemia
B. Erythropoietin deficiency
C. Hemolytic anemia due to oxidative stress
D. Bone marrow fibrosis
E. Microangiopathic hemolytic anemia

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aPTT = activated partial thromboplastin time; PT = prothrombin time.

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This patient's hemarthroses and excessive bleeding following tooth extraction are suggestive of a coagulopathy (ie, clotting factor deficiency). **Coagulopathies** generally present with **deep-tissue bleeding** into joints, muscles, and subcutaneous tissue. In contrast, **platelet defects** typically manifest with **mucocutaneous bleeding** (eg, epistaxis, petechiae). The patient's laboratory results show a normal bleeding time, normal activated partial thromboplastin time (aPTT), and a prolonged prothrombin time (PT). The normal bleeding time indicates adequate platelet function, and the normal aPTT indicates an intact intrinsic coagulation system. However, the **prolonged PT** indicates a defect in the **extrinsic** coagulation pathway. Therefore, the patient is most likely deficient in factor VII.

(Choice B) Factor VIII deficiency results in classic X-linked hemophilia A. Coagulation studies will show a normal bleeding time, normal PT, and prolonged aPTT.

(Choice C) Factor XI deficiency results in a rare autosomal recessive disorder called hemophilia C. Spontaneous bleeding is rare in this condition, but affected patients are at increased risk for bleeding following surgery or trauma. Coagulation studies will show a prolonged aPTT and normal PT.

(Choice D) Hageman factor (factor XII) deficiency is an autosomal recessive disorder that does not typically cause clinically significant bleeding despite aPTT prolongation.

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